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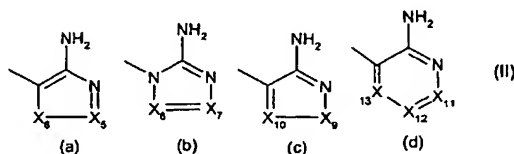
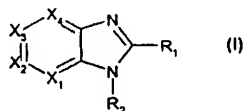
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(54) Title: IMIDAZOPYRIDINE DERIVATIVES AS KINASE INHIBITORS



(57) Abstract: A compound of the formula: (I) and-physiologically acceptable salts and or N-oxides thereof wherein, X<sub>1</sub> is N or CR<sub>3</sub>; X<sub>2</sub> is N or CR<sub>4</sub>; X<sub>3</sub> is N or CR<sub>5</sub>; X<sub>4</sub> is N or CR<sub>6</sub> with the proviso that at least one but not more than two of X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, and X<sub>4</sub> represents N. R<sub>1</sub> is a 5-, or 6-membered heterocyclic group selected from group a, b, c or d formula: (II) wherein X<sub>5</sub> is a group selected from N or CR<sub>7</sub>; and X<sub>6</sub>, is a group selected from O, S or NR<sub>8</sub>; X<sub>7</sub> and X<sub>8</sub>, which maybe the same or, different is a group selected from N or CR<sub>9</sub>; X<sub>9</sub>, is a group selected from O, S or NR<sub>8</sub> and X<sub>10</sub> is N or CR<sub>10</sub>; X<sub>11</sub>, X<sub>12</sub> and X<sub>13</sub> may be the same or different and selected from a group N or CR<sub>11</sub>; processes for their preparation, pharmaceutical compositions containing them and their use in medicine.



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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

## IMIDAZOPYRIDINE DERIVATIVES AS KINASE INHIBITORS

The present invention relates to novel imidazopyridine derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

- 5 More particularly the present invention relates to novel imidazopyridine derivatives which are inhibitors of kinases and in particular of mitogen and stress activated protein kinase-1 (herein after referred to as Msk-1) and or Rho-kinase 1 and or 2 (herein after referred to as ROCK 1 and 2).

- 10 An important mechanism by which cells sense and respond to extracellular stimuli is the activation and modulation of intracellular signal transduction pathways. One of the major signal transduction systems utilized by cells is the MAPK signalling pathways. These pathways share a common architecture, consisting of a cascade of protein kinases that are sequentially phosphorylated and activated, resulting in the activation of a MAP kinase (MAPK). Three MAP kinase pathways have been widely characterised: the Erk pathway, 15 which responds to mitogenic stimuli and results in activation of Erk, and the JNK and p38 pathways, which are commonly associated with transducing cellular stress signals and result in activation of JNK and p38 MAPK.

- Mitogen and stress-activated protein kinases 1 (Msk1) and 2 (Msk2, also named RSKB or RLPK) constitute a family of kinases that can be phosphorylated and activated by 20 either p38 or Erk. Msks are reported to be localized exclusively to the nucleus, and are responsible for the phosphorylation and activation of the transcription factor CREB in response to certain stress stimuli. In macrophage and monocyte cells, Msk1 is involved in CREB-mediated transcriptional regulation of IL-1 $\beta$  and Cox2 in response to bacterial lipopolysaccharide. In addition, Msk1 can also phosphorylate the nucleosomal proteins 25 histone H3 and HMG14, and thus may have a critical role in linking cellular signalling pathways to chromatin modification and modulation of transcription factor complexes.

Inhibitors of kinases in the Erk MAPK cascade have been suggested for use in the treatment and/or prophylaxis of disorders associated with neuronal degeneration resulting from ischemic events, including cerebral ischemia after cardiac arrest, stroke and multi-infarct dementia and also after cerebral ischemic events such as those resulting from head injury, surgery and/or during childbirth. Since Msks are activated by Erk MAPK, Msk inhibitors could serve a similar use. Although Msks are only one of a number of Erk substrates, CREB is involved in many different transcriptional activities, and Msk-mediated CREB phosphorylation could play a role in some cancers. In addition, through modulation of production of pro-inflammatory cytokines such as IL-1 $\beta$  and prostaglandins, inhibitors of Msks could be of use in treatments for neuroinflammatory diseases such as stroke, multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and inflammatory pain, as well as other inflammatory diseases such as rheumatoid arthritis, irritable bowel syndrome, inflammatory bowel disease and asthma.

Another of the major signal transduction systems utilized by cells is the RhoA-signalling pathways. RhoA is a small GTP binding protein that can be activated by several extracellular stimuli such as growth factor, hormones, mechanic stress, osmotic change as well as high concentration of metabolite like glucose. RhoA activation involves GTP binding, conformation alteration, post-translational modification (geranylgeranyllization and farnesylation) and activation of its intrinsic GTPase activity. Activated RhoA is capable of interacting with several effector proteins including ROCKs and transmit signals into cellular cytoplasm and nucleus.

ROCK1 and 2 constitute a family of kinases that can be activated by RhoA-GTP complex via physical association. Activated ROCKs phosphorylate a number of substrates and play important roles in pivotal cellular functions. The substrates for ROCKs include myosin binding subunit of myosin light chain phosphatase (MBS, also named MYPT1), adducin, moesin, myosin light chain (MLC), LIM kinase as well as transcription factor FHL. The phosphorylation of these substrates modulate the biological activity of the proteins and



thus provide a means to alter cell's response to external stimuli. One well documented example is the participation of ROCK in smooth muscle contraction. Upon stimulation by phenylephrine, smooth muscle from blood vessels contracts. Studies have shown that phenylephrine stimulates  $\alpha$ -adrenergic receptors and leads to the activation of RhoA.

- 5 Activated RhoA in turn stimulates kinase activity of ROCK1 and which in turn phosphorylates MBS. Such phosphorylation inhibits the enzyme activity of myosin light chain phosphatase and increases the phosphorylation of myosin light chain itself by a calcium-dependent myosin light chain kinase (MLCK) and consequently increases the contractility of myosin-actin bundle, leading to smooth muscle contraction. This phenomena is also sometimes
- 10 called calcium sensitization. In addition to smooth muscle contraction, ROCKs have also been shown to be involved in cellular functions including apoptosis, cell migration, transcriptional activation, fibrosis, cytokinesis, inflammation and cell proliferation. Moreover, in neurons ROCK plays a critical role in the inhibition of axonal growth by myelin-associated inhibitory factors such as myelin-associated glycoprotein (MAG). ROCK-activity also
- 15 mediates the collapse of growth cones in developing neurons. Both processes are thought to be mediated by ROCK-induced phosphorylation of substrates such as LIM kinase and myosin light chain phosphatase, resulting in increased contractility of the neuronal actin-myosin system..

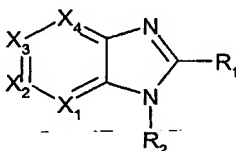
- Inhibitors of ROCKs have been suggested for use in the treatments of a variety of
- 20 diseases. They include cardiovascular diseases such as hypertension, chronic and congestive heart failure, cardiac hypertrophy, restenosis, chronic renal failure and atherosclerosis. In addition, because of its muscle relaxing properties, it is also suitable for asthma, male erectile dysfunctions, female sexual dysfunction and over-active bladder syndrome. ROCK inhibitors have been shown to possess anti-inflammatory properties. Thus
- 25 they can be used as treatment for neuroinflammatory diseases such as stroke, multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and inflammatory pain, as well as other inflammatory diseases such as rheumatoid arthritis,

irritable bowel syndrome, inflammatory bowel disease. . In addition, based on their neurite outgrowth inducing effects, ROCK inhibitors could be useful drugs for neuronal regeneration, inducing new axonal growth and axonal rewiring across lesions within the CNS. ROCK inhibitors are therefore likely to be useful for regenerative (recovery) treatment of CNS disorders such as spinal cord injury, acute neuronal injury (stroke, traumatic brain injury), Parkinsons disease, Alzheimers disease and other neurodegenerative disorders. Since ROCK inhibitors reduce cell proliferation and cell migration, they could be useful in treating cancer and tumor metastasis. Further more, there is evidence suggesting that ROCK inhibitors suppress cytoskeletal rearrangement upon virus invasion, thus they also have potential therapeutic value in anti-viral and anti-bacterial applications. ROCK inhibitors are also useful for the treatment of insulin resistance and diabetes.

WO 97/12615 teaches novel 2-heteroaryl benzimidazole derivatives, which are inhibitors of the specific lipoxygenase enzyme 15-LO.

We have now identified a group of novel imidazopyridine derivatives which are potent inhibitors of the protein kinase Msk-1 and or Rho-associated kinase 1 and or 2.

The present invention thus provides compounds of the general formula (I)



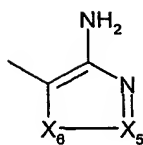
(I)

and physiologically acceptable salts and or N-oxides thereof wherein,

X<sub>1</sub> is N or CR<sub>3</sub>; X<sub>2</sub> is N or CR<sub>4</sub>; X<sub>3</sub> is N or CR<sub>5</sub>; X<sub>4</sub> is N or CR<sub>6</sub>.

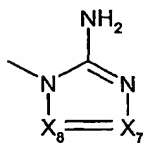
with the proviso that at least one but not more than two of X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub> and X<sub>4</sub> represents N.

R<sub>1</sub> is a 5-, or 6- membered heterocyclic group selected from group a, b, c or d



(a)

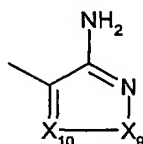
wherein  $X_5$  is a group selected from N or  $CR_7$  and  $X_6$  is a group selected from O, S or  $NR_8$ ,



(b)

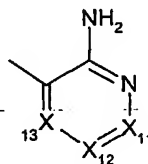
wherein  $X_7$  and  $X_8$  which may be the same or different is a group selected from N or  $CR_8$ ,

5



(c)

wherein  $X_9$  is a group selected from O, S or  $NR_8$  and  $X_{10}$  is N or  $CR_{10}$ ,



(d)

10 wherein  $X_{11}$ ,  $X_{12}$  and  $X_{13}$  may be the same or different and selected from a group N or  $CR_{11}$ ;

$R_2$  and  $R_8$  independently represents hydrogen, hydroxy, aryl, heteroaryl,  $C_{3-7}$

cycloalkyl, heterocyclyl, a group  $YR_{12}$ ,  $N=R_{13}$ ,  $CONR_{14}R_{15}$ ,  $COCH_2NR_{19}R_{20}$ ,  $NR_{14}COR_{16}$ ,

$SO_2NR_{14}R_{15}$  or  $C_{1-6}$ alkyl [optionally substituted by a group selected from optionally

substituted phenyl,  $C_{3-7}$ cycloalkyl, heteroaryl, heterocyclyl, acylamino,  $NH_2$ ,  $R_{19}NH$ ,  $R_{19}R_{20}N$ ,

SO<sub>2</sub>NR<sub>14</sub>R<sub>15</sub>, CONR<sub>14</sub>R<sub>15</sub>, NR<sub>14</sub>COR<sub>16</sub>, OalkNR<sub>19</sub>R<sub>20</sub>, SalkNR<sub>19</sub>R<sub>20</sub> or NR<sub>17</sub>SO<sub>2</sub>R<sub>18</sub> group];

R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>9</sub>, R<sub>10</sub> and R<sub>11</sub> independently represent a group selected from hydrogen, halogen, hydroxy, R<sub>19</sub>O, R<sub>19</sub>S(O)<sub>n</sub>, NH<sub>2</sub>, R<sub>19</sub>NH, R<sub>19</sub>R<sub>20</sub>N, nitro, formyl, C<sub>1</sub>-

5 4alkanoyl, alkenyl (optionally substituted by optionally substituted phenyl, heterocyclyl, or heteoaryl), carboxy, optionally substituted phenyl, heteroaryl, cycloalkyl, cycloalkylalkyl, aryloxy, heteroaryloxy, heterocyclyl, CONR<sub>14</sub>R<sub>15</sub>, NR<sub>14</sub>COR<sub>16</sub>, SO<sub>2</sub>NR<sub>14</sub>R<sub>15</sub>, NR<sub>17</sub>SO<sub>2</sub>R<sub>18</sub> or C<sub>1-6</sub>alkyl [optionally substituted by a group selected from optionally substituted phenyl, C<sub>3</sub>-  
7cycloalkyl, heteroaryl, heterocyclyl, NH<sub>2</sub>, R<sub>19</sub>NH, R<sub>19</sub>R<sub>20</sub>N, acylamino, hydroxy, CONR<sub>14</sub>R<sub>16</sub>,  
10 NR<sub>14</sub>COR<sub>16</sub>, SO<sub>2</sub>NR<sub>14</sub>R<sub>15</sub>, NR<sub>17</sub>SO<sub>2</sub>R<sub>18</sub>, OalkNR<sub>19</sub>R<sub>20</sub>, or SalkNR<sub>19</sub>R<sub>20</sub> group];

R<sub>19</sub> and R<sub>20</sub> independently represent a group selected from C<sub>1-6</sub> alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>3</sub>-  
7cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl;

Y represents O, NH, NR<sub>12</sub> or S(O)<sub>n</sub>;

R<sub>12</sub> represents aryl, heteroaryl, cycloalkyl, heterocyclyl or C<sub>1-6</sub>alkyl [optionally  
15 substituted by a group selected from optionally substituted phenyl, C<sub>3-7</sub>cycloalkyl, heteroaryl, heterocyclyl, NH<sub>2</sub>, R<sub>19</sub>NH, R<sub>19</sub>R<sub>20</sub>N, acylamino, hydroxy, CONR<sub>14</sub>R<sub>15</sub>, NR<sub>14</sub>COR<sub>16</sub>,  
SO<sub>2</sub>NR<sub>14</sub>R<sub>15</sub>, NR<sub>17</sub>SO<sub>2</sub>R<sub>18</sub>, OalkNR<sub>19</sub>R<sub>20</sub>, or SalkNR<sub>19</sub>R<sub>20</sub> group];

R<sub>13</sub> represents an alkylidene group which may be substituted by an aryl, heteroaryl, heterocyclyl or cycloalkyl group or R<sub>13</sub> represents a cycloalkylidene or heterocycloalkylidene  
20 group.

R<sub>14</sub> and R<sub>15</sub> independently represent hydrogen, aryl, heteroaryl, cycloalkyl or C<sub>1-6</sub>alkyl [optionally substituted by a group selected from optionally substituted phenyl, C<sub>3-7</sub>cycloalkyl, heteroaryl, heterocyclyl, NH<sub>2</sub>, R<sub>19</sub>NH, R<sub>19</sub>R<sub>20</sub>N, or acylamino group] or R<sub>14</sub> and R<sub>15</sub> together  
25 saturated or unsaturated and optionally contains another heteroatom selected from O, N or S(O)<sub>n</sub>;

$R_{16}$  and  $R_{18}$  independently represent ,aryl, heteroaryl, heterocyclyl, cycloalkyl or  $C_{1-6}$ alkyl [optionally substituted by a group selected from optionally substituted phenyl,  $C_{3-7}$ cycloalkyl, heteroaryl, heterocyclyl,  $NH_2$ ,  $R_{19}NH$ ,  $R_{19}R_{20}N$  , or acylamino group] or the group  $NR_{14}R_{15}$  wherein  $R_{14}$  and  $R_{15}$  have the meanings defined above;

5  $R_{17}$  represents hydrogen, aryl, heteroaryl, heterocyclyl, cycloalkyl or  $C_{1-6}$ alkyl [optionally substituted by a group selected from optionally substituted phenyl,  $C_{3-7}$ cycloalkyl, heteroaryl, heterocyclyl,  $NH_2$ ,  $R_{19}NH$ ,  $R_{19}R_{20}N$  , or acylamino group];

Alk is a  $C_{2-4}$  straight or branched alkylene chain

n is zero, 1 or 2.

10 It will be appreciated that any of the substituents  $R_1$  to  $R_{20}$  as defined in formula (1) above may contain at least one asymmetric center and it is to be understood that the invention includes all possible enantiomers arising therefrom and mixtures thereof including racemates.

The term alkyl as a group or part of a group e.g. alkoxy, alkylthio, alkylamino  
15 ,dialkylamino, optionally substituted alkyl e.g. aminoalkyl, cycloalkylalkyl, aralkyl, heteroarylalkyl or heterocyclalkyl refers to a  $C_{1-6}$  straight or branched chain alkyl group.

The term halogen includes fluorine, chlorine, bromine or iodine.

The term aryl as a group or part of a group e.g. aryloxy, aralkyl or arylamino refers to an optionally substituted phenyl or fused bicyclic aryl group e.g. naphthyl.

20 The terms aryl, optionally substituted phenyl, heteroaryl,  $C_{3-7}$  cycloalkyl as a group or part of a group and 4-7 membered heterocyclyl as a group or part of a group includes such groups which are optionally substituted with 1 to 3 substituents which may be the same or different and selected from halogen, aryl, heteroaryl, heterocyclalkyl, hydroxy, alkyl, alkoxy, trifluoroalkyl, amino, alkylamino , dialkylamino, arylamino, heteroarylamino,  
25 heterocyclamino, acylamino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, acylaminoalkyl, arylaminoalkyl, heteroarylaminoalkyl, cycloalkylaminoalkyl, heterocyclaminoalkyl, hydroxyalkyl,  $CONR_{14}R_{15}$ ,  $CH_2CONR_{14}R_{15}$  carboxy, carboxamido, alkoxycarbonyl,

aminoalkoxy, dialkylaminoalkoxy, acylaminoalkoxy, sulphonamido, aminosulphonyl, cyano, formyl, nitro,  $R_{21}O$  or  $R_{21}S(O)_n$  wherein  $R_{21}$  is a group selected from alkyl, aryl, heteroaryl or heterocyclylalkoxy and  $n$  is zero, one or two, or each of the said groups form part of a fused bicyclic ring system containing up to 10 ring members and which is at least partially

5 saturated.

The term heteroaryl as a group or part of a group e.g. heteroaryloxy refers to a 5, or 6 membered ring or a fused 5,6 or 6,6 bicyclic ring system.

When heteroaryl represents a 5 membered group it contains a heteroatom selected from O, N or S and may optionally contain a further 1 to 3 nitrogen atoms. Examples of such groups  
10 include furanyl, thienyl, isoxazolyl, oxazolyl or imidazolyl.

When heteroaryl represents a 6-membered group it contains from 1 to 3 nitrogen atoms. Examples of such groups include pyridyl, pyrimidinyl, or triazinyl.

The term 5,6 fused bicyclic heteroaryl group refers to a group in which the 5-membered ring contains an oxygen, sulphur or NH group and the 6 membered ring optionally contains from  
15 1 to 3 nitrogen atoms. Examples of such groups include benzofuranyl, benzothienyl or indolyl.

The term 6,6-fused bicyclic heteroaryl group refers to a bicyclic heteroaryl group which contains at least one nitrogen atom in one of the rings and may contain up to 3 nitrogen atoms in each ring. Examples of such groups include quinolinyl, isoquinolinyl or  
20 naphthyridinyl also the term 6,6 fused bicyclic heteroaryl group refers to a 6-membered heteroaryl group which is fused to a partially saturated carbocyclic group. Examples of such a group includes tetrahydroquinolinyl or tetrahydroisoquinolinyl.

The term heterocyclyl as a group or part of a group e.g. heterocyclylalkyl or heterocyclylalkylidene refers to a bridged heterocyclic group or a 4-7 membered  
25 heterocyclyl group which is linked to the rest of the compound of formula (1) via a carbon or nitrogen atom in that group and which contains one or two hetero atoms selected from N, O or  $S(O)_n$ , and when the heterocyclyl group contains a ring member NH or the heterocyclyl

group is substituted by a primary or secondary amino group then the term also includes N-alkyl, N-optionally substituted phenyl, N-benzyl or, N-acyl derivatives thereof. The term heterocyclic also includes bridged heterocyclic. Examples of such heterocyclic groups include optionally substituted pyrrolidine, piperidine, piperazine homopiperazine, morpholine, thiomorpholine and (8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-amine

The term cycloalkyl as a group or part of a group e.g. cycloalkylalkyl or cycloalkylidene refers to a 3-7 membered carbocyclic group.

The term fused bicyclic ring system containing up to 11 ring members and which is at least partially saturated includes carbocyclic and heterocyclic 6,5,6,6 and 6,7 bicyclic ring systems. Examples of such 6,5 and 6,6 carbocyclic ring systems include those wherein the bicyclic ring comprises a benzene ring fused to a 5-, 6- or 7-membered carbocyclic ring which is at least partially saturated e.g. tetrahydronaphthyl, indanyl or indenyl. Examples of such 6,5, 6,6 or 6,7 heterocyclic rings include those wherein one ring is benzene which is fused to a 5, 6 or 7 membered ring containing one or two hetero atoms selected from O, S or N e.g. indolinyl, isoindolinyl, 2,3-dihydro-1H-isoindol-5-yl, dihydrobenzofuranyl, dihydrobenzothienyl, 1,3-benzodioxolyl, benzopyrrolyl, 1,3-benzodithioly, 1,4-benzodioxanyl, chromanyl, chromenyl or 2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yl.

The term acyl as a group or part of the acylamino group refers to an alkanoyl, aroyl, aralkanoyl, alkoxycarbonyl, aryloxycarbonyl or aralkoxycarbonyl group.

The compounds of formula (I) form salts with inorganic and organic acids and the invention includes such salts formed with physiologically acceptable inorganic and organic acids.

The compounds of formula (I), form N-oxides. Thus, the compound of formula (I) wherein  $X_3$  is N or  $X_2$  is N forms an N oxide and the invention includes such compounds.

A preferred class of compounds of formula (I) are those wherein only one of  $X_1$ ,  $X_2$ ,  $X_3$  or  $X_4$  represents N. Within this class conveniently  $X_2$  or  $X_3$  represent N or more particularly  $X_3$  represents N.

A further preferred class of compounds are those wherein  $X_1$  and  $X_3$  each represents N.

A further preferred class of compounds of formula (I) are those wherein  $R_1$  is a group selected from (c) or (d).

5 A preferred group of compounds according to the invention are those of formula (I) wherein  $X_3$  is N,  $X_1$  is  $CR_3$ ,  $X_2$  is  $CR_4$  and  $X_4$  is  $CR_6$ .

$R_1$  is a group c wherein  $X_9$  is O and  $X_{10}$  is N; Within this group a preferred class are those wherein  $R_2$  is hydrogen, optionally substituted alkyl, aryl, heteroaryl,  $C_{3-7}$ cycloalkyl or heterocyclyl,

10  $R_3$  represent a group selected from hydrogen, halogen,  $R_{19}O$ ,  $R_{19}S(O)_n$ ,  $R_{19}NH$ ,  $R_{19}R_{20}N$ , carboxyl,  $CONR_{14}R_{15}$ ,  $SO_2NR_{14}R_{15}$ , optionally substituted phenyl, heteroaryl,  $C_{1-6}$ alkyl, or methyl [substituted by a group selected from optionally substituted phenyl,  $R_{19}NH$ ,  $R_{19}R_{20}N$ ,  $CONR_{14}R_{15}$ ,  $SO_2NR_{14}R_{15}$ ,  $R_{19}O$  or  $R_{19}S(O)_n$ ,  $R_4$  represents hydrogen, halogen, optionally substituted  $C_{1-4}$ alkyl,  $R_{19}O$ ,  $R_{19}S(O)_n$ ,  $R_{19}NH$  or  $R_{19}R_{20}N$ ;  $R_6$  represents hydrogen, 15 halogen, optionally substituted  $C_{1-6}$ alkyl, optionally substituted phenyl,  $R_{19}NH$ ,  $R_{19}R_{20}N$ ,  $R_{19}O$  or  $R_{19}S(O)_n$  or methyl substituted by optionally substituted phenyl.

When  $R_1$  is the group (c) this is conveniently a group wherein  $X_9$  is oxygen and  $X_{10}$  is nitrogen or  $X_9$  is  $NR_8$  wherein  $R_8$  is hydrogen or methyl and  $X_9$  is CH

When  $R_1$  is the group (d) this is conveniently a group wherein  $X_{11}$  and  $X_{12}$  each 20 represent CH and  $X_{13}$  is the group CH or N.

The group  $R_1$  is preferably a group (c) wherein  $X_9$  is oxygen and  $X_{10}$  is nitrogen.

Examples of suitable  $R_2$  groups include hydrogen,  $C_{1-6}$ alkyl such as methyl, ethyl, isopropyl, sec butyl and 2-ethylbutyl,  $C_{3-7}$  cycloalkyl e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl,  $C_{3-7}$ cycloalkylalkyl e.g.  $C_{3-7}$  cycloalkylmethyl such as 25 cyclopropylmethyl or cyclohexylmethyl, optionally substituted phenyl such as phenyl or phenyl substituted by [amino eg 4-aminophenyl, dialkylamino, eg dimethylamino, dialkylaminoalkylamino (eg dimethylaminoethylamino, N-methyl, dimethylaminoethylamino,



N,N-bis(2-dimethylaminoethyl)amino), alkyl eg ethyl, alkanoyl eg acetyl, alkoxy (eg methoxy or 3-methylbutoxy) halo, (eg chlorine or bromine, hydroxy, aminoalkyl eg aminomethyl, hydroxalkoxy (eg 2-hydroxyethoxy or 3-hydroxypropoxy), aminoalkoxy eg 2- aminoethoxy, alkylaminoalkoxy eg 2-methylaminoethoxy, dialkylaminoethoxy (eg 2-dimethylaminoethoxy, 2 diethylaminoethoxy, 2 diethylamino-1-methylethoxy, 2-disopropylamino-1-methylethoxy),  
 5 N-alkyl-N-alkylaminoalkoxy eg N-benzyl N-methylaminoethoxy, aminocarbonylalkoxy eg (aminocarbonylmethoxy, aminocarbonyl-2-methylethoxy, aminocarbonylethoxy), alkylaminocarbonylalkoxy eg methylaminocarbonylmethoxy, dialkylaminocarbonylalkoxy, eg dimethylaminocarboxymethoxy, ureidoalkoxy eg ureidomethoxy, alkylureido eg 3-methylureido, dialkylamino-acetamido eg dimethylaminoacetamido, alkylthioalkoxy eg methylthiomethoxy, phenylthioalkoxy eg phenylthiomethoxy, alkylsulphanylalkoxy eg methylsulphanylalkoxy, phenylsulphanylalkoxy eg phenylsulphanylalkoxy, alkylsulphonylalkoxy eg methylsulphonylalkoxy, phenylsulphonylalkoxy eg phenylsulphonylalkoxy, cyanoalkoxy eg cyanomethoxy or 2-cyanoethoxy, acylaminoethoxy  
 10 eg (t butoxycarbonylaminoethoxy, isoxazolylaminoethoxy, isonicotinylaminoethoxy, alkylsulphonylamino-alkoxy eg methylsulphonylaminoethoxy, phenylsulphonylaminoalkoxy eg phenylsulphonylaminoethoxy, alkoxycarbonylalkoxy eg -2methoxycarbonyl 1-methylethoxy, heterocyclylalkoxy eg (morpholinoethoxy, piperidinoethoxy, 1-pyrrolidino-2-ylmethoxy, heterocyclyloxy e.g. 1-methyl-piperidino-4-yloxy, heterocyclyl eg 3-pyrrolidinyl,]  
 20 , alkyl (substituted by hydroxy e.g. 2-hydroxy-1-methyl-ethyl), alkyl substituted by [amino eg (3- aminopropyl, 4-aminobutyl, 5 aminopentyl) , acylamino e.g. 4-butyloxycarbonylamino-butyl , R<sub>19</sub>NH or R<sub>19</sub>R<sub>20</sub>N e.g. (2-dimethylamino-1-methylethyl, 4-diethylamino-1-methyl- butyl or 3-dimethylaminopropyl)], alkyl e.g. methyl or ethyl substituted by a 4-7-membered heterocyclyl group e.g. 4-methylpiperazin-1-ethyl, 2-piperazin-yl-ethyl, piperidine 4-yl methyl or piperidine 3-yl methyl, a 4-7 membered heterocyclyl group such as piperidinyl e.g.  
 25 piperidin-4-yl or piperidin-3-yl or pyrrolidinyl e.g. pyrrolidin-3-yl, a 5,6 fused bicyclic heteroaryl group such as indazolyl e.g. 5-indazolyl or 6- indazolyl, or 6,6 fused bicyclic heterocyclic e.g.

tetrahydroisoquinolin-5-yl, 2-methyl tetrahydroisoquinolin-7-yl, 2-methanesulphonyl-tetrahydroisoquinolin-7-yl or tetrahydroisoquinolin-7-yl, 3,4 dihydro-2H-isoquinolin-1-one-7-yl, a 6,5 fused heterocyclic group e.g. 2,3-dihydro-1H-isoindol-5-yl, or benzo[1,3]dioxol-5-yl or a 6,7 fused heterocyclic e.g. 2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yl.

- 5           When  $X_2$  is  $CR_4$  then the group  $R_4$  is conveniently hydrogen, methyl or alkoxy e.g. methoxy, alkylthio e.g. methylthio, phenylamino or phenoxy optionally substituted by halogen e.g. fluoro or acetamido.

          When  $X_3$  is  $CR_5$  then  $R_5$  is conveniently hydrogen, alkyl e.g. methyl or alkoxy e.g. methoxy or optionally substituted phenoxy e.g. phenoxy..

- 10           Wherein  $X_4$  is  $CR_6$  the group  $R_6$  is conveniently hydrogen, halogen e.g. chlorine, hydroxyalkyl e.g. hydroxymethyl, alkyl e.g. methyl, alkoxy e.g. methoxy, optionally substituted phenyl e.g. phenyl or a 4-7 membered heterocyclyl group e.g. 1- pyrrolidinyl or 1- pyrazolyl

- Wherein  $X_1$  is the group  $CR_3$  then  $R_3$  is conveniently hydrogen, halogen e.g. bromine, hydroxy, carboxyl, optionally substituted phenyl e.g. phenyl or phenyl (substituted by one or
- 15   two groups selected from alkoxy e.g. methoxy or ethoxy, hydroxy, hydroxymethyl, trifluoromethyl, trifluoromethoxy, amino, acetamido, aminoalkyl, e.g. aminomethyl, or aminoethyl, alkyl e.g. methyl or ethyl, carboxyl carboxamido, N,N-dimethylcarboxamido, cyano, formyl, aryloxy e.g. phenoxy  $CH_3S(O)_n$  wherein  $n$  is zero, 1 or 2,  $CH_3SO_2NH$ , or halogen e.g. fluorine), or heterocyclyl e.g. 5-methyl-1,2,4-oxadiazol-3-yl, an heteroaryl group
- 20   e.g. thienyl (optionally substituted by formyl, alkyl eg methyl or phenyl) such as 2-thienyl, 4-methylthienyl, 5-phenylthienyl, 5-formylthienyl, or 3-thienyl, 2-furanyl, pyridyl such as 3-pyridyl or 4-pyridyl, 3,5-dimethylisoxazol-4-yl, indolyl or 8-quinolyl, benzothienyl, a 6,5-fused bicycloheterocyclyl e.g. 5-benzo[1,3]dioxolyl or  $R_3$  is optionally substituted phenyl such as phenyl or halophenyl e.g. fluorophenyl substituted by the group  $CH_2NR_{19}R_{20}$  wherein  $R_{19}$  is
- 25   alkyl e.g. methyl or ethyl, phenyl or a heterocyclic group such as a 4-7 heterocyclic group and  $R_{20}$  is hydrogen or methyl, or  $NR_{19}R_{20}$  is a 4-7 heterocyclic group. Examples of suitable

NR<sub>19</sub>R<sub>20</sub> groups include ethylamino, dimethylamino, 4-morpholino, pyrrolidino, piperidino, piperidin-4-yl-amino or 1-t butoxycarbonyl-piperidin-4-yl-amino. or

R<sub>3</sub> is alkyl substituted by a 4-7 membered heterocyclyl group or a group NR<sub>19</sub>R<sub>20</sub> wherein

R<sub>19</sub> is hydroxylalkyl, optionally substituted benzyl, C<sub>3-7</sub> cycloalkyl, a heterocyclic group

5 e.g. bridge heterocycle, or a 4-7 membered heterocyclyl, 4-7 membered heterocyclalkyl or

C<sub>3-7</sub> cycloalkylalkyl. Conveniently the 4-7 membered heterocyclyl group or moiety is

selected from a 5-7 membered group containing one or 2 ring members selected from

nitrogen or oxygen e.g. pyrrolidinyl, piperidinyl, morpholinyl piperazinyl or homo- piperazinyl.

R<sub>20</sub> is hydrogen, methyl or acetyl. Examples of such R<sub>3</sub> groups include 3-

10 hydroxypropylamino, 4-bromobenzylamino, 4-methoxybenzylamino,

4-piperidinylaminomethyl, N-4-piperidinyl-N-methylaminomethyl, 1-t butyoxycarbonyl-piperidinyl-aminomethyl

4-aminopiperidinomethyl, 1,4-diazepan-1-ylmethyl, piperazinomethyl, 4-

methylpiperazinomethyl, 4-acetyl piperizin-1-ylmethyl, 4-ethylpiperazinomethyl

15 4-morpholinomethyl, piperidinomethyl, 4-(methylamino)piperidinomethyl, 4-

cyclopropylaminopiperidinomethyl, pyrrolidinomethyl, 3-dimethylaminopyrrolidinomethyl, 2-

hydroxymethylpyrrolidinomethyl, 4-ethylpiperazino-methyl, 3-pyrrolidin-1-yl-

propylaminomethyl, 4-(4-fluorophenyl) piperazinomethyl, 3-piperidinyl-1-yl-

propylaminomethyl, 3-morpholin-4-yl-propylaminomethyl, 3-(4-methylpiperazin-yl

20 propylaminomethyl, 1-methyl piperidin-4-yl-aminomethyl, 4-pyrrolidinocarbonylmethyl-

piperazinomethyl, 2-pyrrolidin-1-ylmethylpyrrolidinomethyl, 2-pyrrolidin-1-yl-

ethylaminomethyl, 3-dimethylaminopyrrolidinomethyl, 1-methyl-piperidin-4-ylaminomethyl, 1-

isopropyl-piperidin-4-ylaminomethyl, 3-dimethylaminopyrrolidinomethyl, 2-(morpholin-yl-

methyl)-pyrrolidinomethyl, 3-piperidin-1-yl-propylaminomethyl, 3-morpholin-4-yl-

25 propylaminomethyl, 3-(4-methylpiperazin-1-yl)propylaminomethyl,

piperidin-1-ylmethylpyrrolidinomethyl, 3,5-dimethylpiperazinomethyl, pyrrolidin-1-

ylpiperidinomethyl, pyrrolidino-3-ylaminomethyl, pyrrolidin-2-ylmethylaminomethyl,

- 4-aminomethylcyclohexylmethylaminomethyl, 4-aminocyclohexylaminomethyl, 2-piperazin-1-ylethylaminomethyl, 3-amino-pyrrolidinomethyl, pyrrolidino-2-ylmethylaminomethyl, piperidin-4-ylmethylaminomethyl, 4-aminomethylpiperidinomethyl, 4-(cyclopropylaminopiperidinomethyl,
- 5 3-(piperazino-1-yl) propylaminomethyl, 2-(morpholin-4-ylmethyl)pyrrolidinomethyl 2-(piperidin-1-ylmethyl)pyrrolidinomethyl, 2-(piperazin-1-ylmethyl)pyrrolidinomethyl, piperidin-4-ylmethyl, N-piperidin-4-yl-acetamidomethyl, or R<sub>3</sub> is 4-heterocycloxy e.g. piperidin-4-yloxy, or heterocyclylalkoxy e.g. piperidin-4-ylmethoxy, or
- 10 R<sub>3</sub> is vinyl optionally substituted by optionally substituted phenyl e.g. 4-methoxystyryl or R<sub>3</sub> is the group CONR<sub>14</sub>R<sub>15</sub> wherein R<sub>15</sub> is hydrogen, R<sub>14</sub> is benzyl, phenethyl, aminoalkyl e.g. 3-aminopropyl 4-aminobutyl or 6-aminoethyl or is a 4-7 membered heterocyclyl group. Conveniently the heterocyclyl group is a 5-6 membered group in which one ring member is nitrogen which
- 15 may be substituted by an aminoalkylcarbonyl group. Suitable examples include piperidinyl e.g. 3 or 4-piperidinyl 1-aminomethylcarbonyl-piperidin-4-yl, or pyrrolidinyl e.g. 3-pyrrolidinyl or R<sub>14</sub> is a 4-7 membered heterocyclylalkyl group. Conveniently the heterocyclic moiety is a 5-7 membered group containing a nitrogen atom and another hetero member selected from oxygen or nitrogen. Suitable examples of such heterocyclylalkyl groups include
- 20 piperidinylmethyl e.g. piperidin-2-ylmethyl or piperidin-4-ylmethyl, morpholinylmethyl e.g. morpholin-2-ylmethyl or piperazinoethyl, or R<sub>14</sub> and R<sub>15</sub> together with the nitrogen atom to which they are attached represent a 4-7 membered heterocyclyl group. Conveniently the heterocyclyl group is a 5-7 membered group which may contain an additional hetero member selected from oxygen, nitrogen or substituted nitrogen Examples of such groups include
- 25 piperazino, 1-methylpiperazino, 4-(2-aminoethyl)piperazino, 4-(t-butoxycarbonylaminoethyl)piperazino, 4-aminoalkylcarbonylpiperazino, e.g. 4-aminomethylcarbonylpiperazino, 4-aminoethylcarbonylpiperazino, 4-1-

(aminoethylcarbonylpiperazino, 4-(1-methylaminoethylcarbonylpiperazino, 4-pyrrolidin-2-yl-carbonylpiperazino, pyrrolidino, 3-aminopyrrolidino, 2-methoxycarbonylpyrrolidino, morpholino, 2 (pyrrolidin-1-yl)methyl pyrrolidino or  $R_3$  is a group  $R_{19}S(O)_n$  wherein  $n$  is zero, 1 or 2 and  $R_{19}$  is optionally substituted phenyl eg phenyl optionally substituted by methoxy or

5 heteroaryl and conveniently  $n$  is zero, or  $R_3$  is a group  $R_{19}NH$  and  $R_{19}$  is optionally substituted phenyl or heteroaryl e.g. phenyl, 4- morpholinophenyl or 3-aminopyridyl.

Examples of suitable compounds according to the invention include those whose preparation is specifically described in examples 1 to 316.

Specific preferred compounds according to the invention include:

- 10 2-(4-amino-furazan-3-yl)-1-ethyl-N-[(2R)-2-morpholinylmethyl]-1H-imidazo[4,5-c]pyridine-7-carboxamide
- 2-(4-amino-furazan-3-yl)-1-ethyl-N-[(2S)-2-morpholinylmethyl]-1H-imidazo[4,5-c]pyridine-7-carboxamide
- 4-{6-[(4-fluorophenyl)oxy]-1-[4-(methyloxy)phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-
- 15 ylamine hydrochloride
- 4-{1-(4-{[2-(dimethylamino)ethyl]oxy}phenyl)-6-[(4-fluorophenyl)oxy]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine hydrochloride
- 2-(4-amino-furazan-3-yl)-1-(cyclopropylmethyl)-N-(2-morpholinylmethyl)-1H-imidazo[4,5-c]pyridine-7-carboxamide hydrochloride
- 20 4-[1-ethyl-6-(methyloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine
- 4-[1-ethyl-6-(methylthio)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine
- 4-[1-ethyl-6-(phenyloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine
- 4-{1-ethyl-6-[(4-fluorophenyl)oxy]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine
- N-(3-{[2-(4-amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-6-yl]oxy}phenyl)acetamide
- 25 hydrochloride
- N-(4-{[2-(4-amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-6-yl]oxy}phenyl)acetamide hydrochloride

- 2-(4-amino-furazan-3-yl)-1-ethyl-N-phenyl-1H-imidazo[4,5-c]pyridin-6-amine  
4-[1-(phenylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine hydrochloride  
4-[1-(2,2,2-trifluoroethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine  
4-[1-(4-fluorophenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-amine hydrochloride
- 5 4-(6-bromo-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine  
4-{7-bromo-1-[4-(methyloxy)phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine  
4-[2-(4-amino-furazan-3-yl)-7-bromo-1H-imidazo[4,5-c]pyridin-1-yl]phenol  
4-[1-(4-{[2-(dimethylamino)ethyl]oxy}phenyl)-7-phenyl-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine
- 10 4-(7-bromo-1-phenyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine  
4-(1,7-diphenyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine  
4-[1-phenyl-7-(2-thienyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine  
4-[2-(4-amino-furazan-3-yl)-1-phenyl-1H-imidazo[4,5-c]pyridin-7-yl]phenol  
2-(4-amino-furazan-3-yl)-1-phenyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid
- 15 4-(7-{4-[(ethylamino)methyl]phenyl}-1-phenyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine  
4-[7-(3,5-dimethyl-4-isoxazolyl)-1-phenyl-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine  
4-{1-ethyl-7-[3-(ethyloxy)phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine hydrochloride
- 20 2-(4-amino-furazan-3-yl)-1-ethyl-N-methyl-1H-imidazo[4,5-c]pyridine-7-sulfonamide hydrochloride  
2-(4-amino-furazan-3-yl)-1-ethyl-N,N-dimethyl-1H-imidazo[4,5-c]pyridine-7-sulfonamide hydrochloride  
{3-[2-(4-amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]phenyl}methanol
- 25 hydrochloride  
4-(1-ethyl-7-{4-[(phenylamino)methyl]phenyl}-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine

- 4-[1-ethyl-7-(2-fluorophenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine hydrochloride
- 4-{1-ethyl-7-[4-(methylsulfonyl)phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine hydrochloride
- 4-{1-ethyl-7-[4-(trifluoromethyl)phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine
- 5 hydrochloride
- 4-[7-(2,4-difluorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine hydrochloride
- 5-[2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]-thiophen-2-yl)-carbaldehyde
- 10 4-[7-(1-benzothien-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine hydrochloride
- 4-{1-ethyl-7-[2-(trifluoromethyl)phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine hydrochloride
- 4-{1-ethyl-7-[4-(methylthio)phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine
- 15 hydrochloride
- 4-[1-ethyl-7-(4-methyl-2-thienyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine hydrochloride
- 4-[7-(2,6-dimethylphenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine hydrochloride
- 20 5-[2-(4-amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]-2-fluorobenzaldehyde hydrochloride
- 4-[7-(3-aminophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine hydrochloride
- 4-(1-ethyl-7-{3-[(trifluoromethyl)oxy]phenyl}-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine hydrochloride
- 25 1-{3-[2-(4-amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]phenyl}ethanone hydrochloride

- N-{4-[2-(4-amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]phenyl}methanesulfonamide hydrochloride
- 4-[1-ethyl-7-(5-phenyl-2-thienyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine hydrochloride
- 5 4-[7-[3,5-bis(trifluoromethyl)phenyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine hydrochloride
- 4-[1-ethyl-7-[4-fluoro-3-(1-pyrrolidinylmethyl)phenyl]-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine hydrochloride
- 4-[1-ethyl-7-[3-fluoro-4-(1-pyrrolidinylmethyl)phenyl]-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-
- 10 3-ylamine hydrochloride
- 4-(1-ethyl-7-[4-[(ethylamino)methyl]-3-fluorophenyl]-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine hydrochloride
- 4-(7-[[3S]-3-amino-1-pyrrolidinyl]sulfonyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine hydrochloride
- 15 4-[1-ethyl-7-[4-(methylsulfinyl)phenyl]-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine hydrochloride
- 4-[1-ethyl-7-(4-morpholinylcarbonyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine
- 2-(4-amino-furazan-3-yl)-1-ethyl-N-(2-hydroxyethyl)-1H-imidazo[4,5-c]pyridine-7-carboxamide
- 20 4-[1-ethyl-7-(1-piperidinylcarbonyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine
- 2-(4-amino-furazan-3-yl)-1-ethyl-N,N-dimethyl-1H-imidazo[4,5-c]pyridine-7-carboxamide
- 2-(4-amino-furazan-3-yl)-1-ethyl-N-(1-methylethyl)-1H-imidazo[4,5-c]pyridine-7-carboxamide
- 2-(4-amino-furazan-3-yl)-1-ethyl-N-phenyl-1H-imidazo[4,5-c]pyridine-7-carboxamide
- 2-(4-amino-furazan-3-yl)-1-ethyl-N-methyl-1H-imidazo[4,5-c]pyridine-7-carboxamide
- 25 2-(4-amino-furazan-3-yl)-1-ethyl-N-[2-(methyloxy)ethyl]-1H-imidazo[4,5-c]pyridine-7-carboxamide



2-(4-amino-furazan-3-yl)-1-ethyl-N-(2,2,6,6-tetramethyl-4-piperidinyl)-1H-imidazo[4,5-c]pyridine-7-carboxamide

1,1-dimethylethyl [5-({[2-(4-amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]carbonyl}amino)pentyl]carbamate

5 1,1-dimethylethyl 4-{2-[[{2-(4-amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]carbonyl}amino)methyl]phenyl}-1-piperazinecarboxylate

2-(4-amino-furazan-3-yl)-N-[3-(dimethylamino)propyl]-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxamide

10 2-(4-amino-furazan-3-yl)-1-ethyl-N-methyl-N-(phenylmethyl)-1H-imidazo[4,5-c]pyridine-7-carboxamide

2-(4-amino-furazan-3-yl)-1-ethyl-N-[2-(1-methyl-2-pyrrolidinyl)ethyl]-1H-imidazo[4,5-c]pyridine-7-carboxamide

2-(4-amino-furazan-3-yl)-N-[2-(4-chlorophenyl)-1-(hydroxymethyl)ethyl]-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxamide

15 4-(1-ethyl-7-[[4-(phenylmethyl)-1-piperazinyl]carbonyl]-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine

2-(4-amino-furazan-3-yl)-1-ethyl-N-[[4-(methyloxy)phenyl]methyl]-1H-imidazo[4,5-c]pyridine-7-carboxamide

2-(4-amino-furazan-3-yl)-N-(5-aminopentyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxamide

20 trifluoroacetate

2-(4-amino-furazan-3-yl)-1-ethyl-N-[[2-(1-piperazinyl)phenyl]methyl]-1H-imidazo[4,5-c]pyridine-7-carboxamide trifluoroacetate

2-(4-amino-furazan-3-yl)-N-[(1S,5R,7S)-3-aminotricyclo[3.3.1.1~3,7~]dec-1-yl]-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxamide trifluoroacetate

25 2-(4-amino-furazan-3-yl)-N-[[4-chloro-3-(trifluoromethyl)phenyl]methyl]-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxamide

- 4-(1-ethyl-7-[[4-(4-pyridinylmethyl)-1-piperazinyl]carbonyl]-1H-imidazo[4,5-c]pyridin-2-yl)-  
furazan-3-ylamine
- 2-(4-amino-furazan-3-yl)-1-ethyl-N-[2-(4-methyl-1-piperidinyl)ethyl]-1H-imidazo[4,5-  
c]pyridine-7-carboxamide
- 5 2-(4-amino-furazan-3-yl)-1-ethyl-N-{2-[(phenylmethyl)amino]ethyl}-1H-imidazo[4,5-c]pyridine-  
7-carboxamide
- 4-{1-ethyl-7-[(4-ethyl-1-piperazinyl)carbonyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-  
ylamine
- 2-(4-amino-furazan-3-yl)-N-[2-(2,4-dichlorophenyl)ethyl]-1-ethyl-1H-imidazo[4,5-c]pyridine-7-  
10 carboxamide
- 2-(4-amino-furazan-3-yl)-1-ethyl-N-[2-(methylamino)ethyl]-1H-imidazo[4,5-c]pyridine-7-  
carboxamide
- 4-{1-ethyl-7-[4-(4-morpholinylcarbonyl)phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-  
ylamine
- 15 4-[2-(4-amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]-N-(2-  
phenylethyl)benzamide
- 4-{1-ethyl-7-[4-(1-pyrrolidinylcarbonyl)phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-  
ylamine
- 4-[2-(4-amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]-N-  
20 (phenylmethyl)benzamide
- methyl 1-({4-[2-(4-amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-  
yl]phenyl}carbonyl)-L-prolinate
- 4-(1-ethyl-7-{4-[(4-methyl-1-piperazinyl)carbonyl]phenyl}-1H-imidazo[4,5-c]pyridin-2-yl)-  
furazan-3-ylamine
- 25 3-[2-(4-amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]-N-(2-  
phenylethyl)benzamide

- 3-[2-(4-amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]-N-(phenylmethyl)benzamide
- methyl 1-({3-[2-(4-amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]phenyl}carbonyl)-L-prolinate
- 5 4-(1-ethyl-7-{3-[(4-methyl-1-piperazinyl)carbonyl]phenyl}-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine
- 4-{1-ethyl-7-[3-(4-morpholinylcarbonyl)phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine
- 4-[1-ethyl-7-(1-pyrrolidinylcarbonyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine
- 10 2-(4-amino-furazan-3-yl)-1-ethyl-N-phenyl-1H-imidazo[4,5-c]pyridin-7-amine
- 4-[1-ethyl-4-(ethyloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine
- 4-[1-ethyl-4-(methyloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine
- 1-{{2-(4-amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl}methyl}-4-piperidinamine hydrochloride
- 15 [2-(4-amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]methanol
- N-{{2-(4-amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl}methyl}-1-(1-methylethyl)-4-piperidinamine hydrochloride
- 1-{{2-(4-amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl}methyl}-N-methyl-4-piperidinamine hydrochloride
- 20 ((2S)-1-{{2-(4-amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl}methyl}-2-pyrrolidinyl)methanol
- 4-(7-{{{3R}-3-(dimethylamino)-1-pyrrolidinyl}methyl}-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine hydrochloride
- 4-(7-{{{3S}-3-(dimethylamino)-1-pyrrolidinyl}methyl}-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine hydrochloride
- 25 3-({[2-(4-amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]methyl}amino)-1-propanol

- 4-[1-ethyl-7-({[2-(1-piperazinyl)ethyl]amino}methyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine hydrochloride
- 2-(4-amino-furazan-3-yl)-1-ethyl-N-[(3R)-3-pyrrolidinyl]-1H-imidazo[4,5-c]pyridine-7-carboxamide hydrochloride
- 5 2-(4-amino-furazan-3-yl)-1-ethyl-N-[(3S)-3-pyrrolidinyl]-1H-imidazo[4,5-c]pyridine-7-carboxamide hydrochloride
- N-[[2-(4-amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]methyl]-N-4-piperidinylacetamide hydrochloride
- 4-(7-bromo-1-ethyl-4-methyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine
- 10 [2-(4-amino-furazan-3-yl)-7-bromo-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl]methanol hydrochloride
- 4-[1-ethyl-7-({4-[(methylamino)acetyl]-1-piperazinyl}carbonyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine hydrochloride
- 4-(7-{[4-(aminoacetyl)-1-piperazinyl]carbonyl}-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-
- 15 3-ylamine hydrochloride
- 4-(7-{[4-(3-aminopropanoyl)-1-piperazinyl]carbonyl}-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine hydrochloride
- 4-[7-({4-[(2R)-2-aminopropanoyl]-1-piperazinyl}carbonyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine hydrochloride
- 20 4-[7-({4-[(2S)-2-aminopropanoyl]-1-piperazinyl}carbonyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine hydrochloride
- 4-[9-cyclopropyl-2-(methylthio)-9H-purin-8-yl]-furazan-3-ylamine
- 4-[1-(3-Methoxy-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine
- 3-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenol
- 25 1-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenyl}-ethanone oxime
- 4-[1-(2-Methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-1 H-imidazo[4,5-c]pyridin-2-

- yl]-furazan-3-ylamine
- 4-(1-Benzo[1,3]dioxol-5-yl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine
- 7-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-3,4-dihydro-2H-isoquinolin-1-one
- 5 4-[1-(2-Methanesulfonyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine
- 4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-N-hydroxy-benzamidine
- 4-[1-(2,3,4,5-Tetrahydro-1H-benzo[c]azepin-8-yl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine
- 10 4-[1-(1H-Indazol-6-yl)-1H-imidazole[4,5-c]pyridin-2-yl]-furazan-3-ylamine
- 4-[1-(1H-Indazol-5-yl)-1H-imidazole[4,5-c]pyridin-2-yl]-furazan-3-ylamine
- 4-{1-[4-(2-Diethylamino-ethoxy)-phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine hydrochloride
- 4-{1-[4-(3-Dimethylamino-propoxy)-phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine hydrochloride
- 15 4-{1-[4-((S)-1-Pyrrolidin-2-ylmethoxy)-phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine
- 4-{1-[4-(2-Morpholin-4-yl-ethoxy)-phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine hydrochloride
- 20 N-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenyl}-N,N',N'-trimethyl-ethane dihydrochloride
- N-{4-[2-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenyl}-N-(2-dimethylamino-ethyl)-N',N'-dimethyl-ethane-1,2-diamine
- 4-{1-[4-(1-Methyl-piperidin-4-yloxy)-phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine
- 25 4-{1-[4-(3-Dimethylamino-propyl)-phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine

- 4-[1-(4-Dimethylamino-phenyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-furazan-3-ylamine
- {4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-*c*]pyridin-1-yl]-phenoxy}-acetonitrile
- 4-{1-[4-((*S*)-1-Methyl-pyrrolidin-2-ylmethoxy)-phenyl]-1*H*-imidazo[4,5-*c*]pyridin-2-yl}-furazan-3-ylamine
- 5 N-{4-[2-(4-amino-furazan-3-yl)-imidazo[4,5-*c*]pyridin-1-yl]-phenyl}-*C*-dimethylamino-acetamide
- N-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-*c*]pyridin-1-yl]-phenyl}-*N*',*N*'-dimethyl-ethane-1,2-diamine
- 10 4-{1-[3-(2-Dimethylamino-ethyloxy)-phenyl]-1*H*-imidazo[4,5-*c*]pyridin-2-yl}-furazan-3-ylamine
- 4-{1-[3-(3-Dimethylamino-propoxy)-phenyl]-1*H*-imidazo[4,5-*c*]pyridin-2-yl}-furazan-3-ylamine
- 1-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-*c*]pyridin-1-yl]-phenyl}-3-methyl-urea
- 15 4-{1-[3-(1-Methyl-piperin-4-yloxy)-phenyl]-1*H*-imidazo[4,5-*c*]pyridine-2-yl}-furazan-3-ylamine
- 4-{1-[4-(2-Piperidin-1-yl-ethoxy)-phenyl]-1*H*-imidazo[4,5-*c*]pyridin-2-yl}-furazan-3-ylamine
- 20 4-{1-[4-(2-Pyrrolidin-1-yl-ethoxy)-phenyl]-1*H*-imidazo[4,5-*c*]pyridin-2-yl}-furazan-3-ylamine
- 4-{1-[4-(2-Dimethylamino-1-methyl-ethoxy)-phenyl]-1*H*-imidazo[4,5-*c*]pyridin-2-yl}-furazan-3-ylamine
- 4-(1-[4-[2-(Benzyl-methyl-amino)-ethoxy]-phenyl]-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-furazan-3-ylamine
- 25 2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-*c*]pyridin-1-yl]-phenoxy}-acetamide
-

- 2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-N-methyl-acetamide
- 2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-N,N-dimethylacetamide
- 5 2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-ethanol
- 3-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-propan-1-ol
- 3-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-propionitrile
- 10 N-(2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-ethyl)-isonicotinamide
- N-(2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-ethyl)-acetamide
- Isoxazole-5-carboxylic acid (2-{4-[2-(4-amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-ethyl)- amide
- 15 N-(2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-ethyl)-methanesulfonamide
- 2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-propionamide
- 20 2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-2-methyl-propionamide
- (2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-ethyl)-carbamic acid tert-butyl ester
- 4-{1-[4-(2-Methylamino-ethoxy)-phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine
- 25 4-{1-[4-(2-Amino-ethoxy)-phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine

- 4-[1-(4-Methylsulfanylmethoxy-phenyl)-1H-imidazo[4,5]pyridin-2-yl]-furazan-3-ylamine
- 4-[1-(4-Benzenesulfinylmethoxy-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine
- 5 4-[1-(4-Benzenesulfonylmethoxy-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine
- 4-[1-(4-Methanesulfinylmethoxy-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine
- 10 4-[1-(4-Phenylsulfanylmethoxy-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine
- N-(2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]-pyridin-1-yl]-phenoxy}-ethyl)-benzenesulfonamide
- (2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-ethyl)-urea
- 15 N-(2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-ethyl)-benzamide
- 3,5-Dimethyl-isoxazole-4-sulfonic acid (2-{4-[2-(4-amino-furazan-3-yl)-imidazo[4,5-c]-pyridin-1-yl]-phenoxy}-ethyl)-amide
- N-[5-(2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-ethylsulfamoyl)-4-methyl-thiazol-2-yl]-acetamide
- 20 4-[1-(4-Methanesulfonylmethoxy-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine
- N-(2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]-pyridin-1-yl]-phenoxy}-ethyl)-benzenesulfonamide
- 25 4-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]phenoxy}-piperidine-1-carboxylic acid benzyl ester
- 4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenol



- 2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridine-7-carboxylic acid (piperidin-2-ylmethyl) amide
- 2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridine-7-carboxylic acid [1-((*S*)-1-pyrrolidin-2-yl-methanoyl)-piperidin-4-yl]-amide
- 5 2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridine-7-carboxylic acid [1-(2-amino-ethanoyl)-piperidin-4-yl]-amide
- N*-[2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-7-ylmethyl]-cyclohexane-1,4-diamine
- 2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridine-7-carboxaldehyde
- 10 2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridine-7-carboxylic acid [1-(3-amino-propanoyl)-piperidin-4-yl]-amide
- [2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-7-ylmethyl]-piperidin-4-yl-amine
- 4-(4-Chloro-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-furazan-3-ylamine
- 4-{1-Ethyl-7-[(3-piperazin-1-yl-propylamino)-methyl]-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-
- 15 furazan-3-ylamine
- 4-(1-Ethyl-7-[[3-(4-methyl-piperazin-1-yl)-propylamino]-methyl]-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-furazan-3-ylamine
- [2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-7-ylmethyl]-[1-(2-methoxy-ethyl)-piperidin-4-yl]-amine
- 20 4-[1-Ethyl-7-((*R*)-2-piperazin-1-ylmethyl-pyrrolidin-1-ylmethyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-furazan-3-ylamine
- 2
- {3-[2-(4-Amino-furazan-3-yl)-1*H*-imidazo[4,5-*c*]pyridin-1-yl]-propyl}-carbamic acid *tert*-butyl ester
- 25 4-(1-Cyclohexylmethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-furazan-3-ylamine
- [2-(4-Amino-furazan-3-yl)-1-cyclopropyl-1*H*-imidazo[4,5-*c*]pyridin-7-ylmethyl]-piperidin-4-yl-amine

4-[2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-7-ylmethyl]-piperazine-1-carboxylic acid *tert*-butyl ester

4-(3-Ethyl-3*H*-imidazo[4,5-*c*]pyridin-2-yl)-furazan-3-ylamine

3-(1-Ethyl-1 *H*-imidazo[4,5-*c*]pyridin-2-yl)-pyrazin-2-ylamine

5 and physiologically acceptable salts thereof.

The ability of the compounds of formula (I) to antagonise the effect of the kinase Msk-1 may be determined using published procedures such as those described in WO9967283 and WO0127315. Alternatively the following *in vitro* assay may be used .

Thus the Msk-1 antagonist activity was determined using human recombinant Msk-1  
10 expressed in Sf9 cells (WO9967283). The enzyme underwent prior activation by incubation with MAPK (p42), which was removed prior to storage and subsequent assay. The assay of Msk-1 activity involved incubation with peptide substrate and ATP<sup>33</sup>, the subsequent incorporation of P<sup>33</sup> into the peptide was quantified by Scintillation Proximity Assay (SPA - Amersham Pharmacia).

15 For IC<sub>50</sub> determination, test compounds were typically dissolved at 10mM in 100% DMSO, with subsequent serial dilution into 10% DMSO. Compounds were typically assayed over an eleven point dilution range with a concentration in the assay of 10uM to 3nM, in duplicate. IC<sub>50</sub> values were calculated by bespoke curve fitting software.

Assays were performed in clear bottomed, white walled, 384 well plates, in a total  
20 assay volume of 12.5ul. The assays contained: 2nM activated MSK1; 2uM biotinylated peptide (biotin-GRPRTSSFAEG-OH); 20uM ATP; 25Bq per pmole ATP<sup>33</sup>; 50mM Hepes; 10mM MgCl<sub>2</sub>; 0.1mM EDTA; 0.0025% Tween-20; 5mM β-Mercaptoethanol; pH 7.5. The reactions were incubated at 20°C for 60 minutes, then terminated by the addition of 10ul of 200mM EDTA.

25 Streptavidin PVT SPA beads were added to a concentration of 0.2mg per well. The plates were shaken for 10 minutes before centrifugation at 2500 rpm for 10 minutes. P<sup>33</sup> incorporation was quantified by scintillation counting in a Wallac Trilux.

The compounds of the invention are therefore useful in the treatment or prevention of diseases and/or conditions mediated through the kinase Msk-1. Thus the compounds are useful for the treatment or prophylaxis of disorders associated with neuronal degeneration resulting from ischemic events or inflammatory conditions. Examples of such disorders

5 include acute stroke e.g. cerebral stroke, thromboembolic stroke, hemorrhagic stroke and cerebral ischemia, multi infarct dementia , pain, arthritis e.g. rheumatoid arthritis, osteoarthritis, psoriasis, and enteropathic arthritis, multiple sclerosis, Alzheimers disease, Parkinson's disease, amyotrophic lateral sclerosis, spinal cord injury and asthma. The compounds may also be useful for the treatment of irritable bowel syndrome, inflammatory

10 bowel disease and certain cancers.

The invention therefore provides for the use of a compound of formula (I) and/or physiologically acceptable salts thereof for use in therapy and in particular for use as a medicine for inhibiting the effects of the kinase Msk-1.

The invention also provides for the use of a compound of formula (I) and/or a

15 physiologically acceptable derivative or salt thereof for the manufacture of a medicament for inhibiting the effects of the kinase Msk-1

According to a further aspect, the invention also provides for a method for inhibiting the effects of the kinase Msk-1 in a mammal e.g. a human , comprising administering to a patient in need thereof an effective amount of a compound of formula (I) and/or a

20 physiologically acceptable derivative or salt thereof.

The ability of the compounds of formula (I) to antagonise the effect of the kinase ROCK1 may be determined by using the following assays:

1. ROCK kinase assay:

ROCK inhibitor activity was determined using human recombinant ROCK1 kinase

25 domain (amino acid 1-578) expressed in Sf9 cells (WO9967283). The enzyme was purified using his-tag NTA column and Source15 HPLC chromatography. The assay of Rock-1 activity involved incubation with peptide substrate and ATP<sup>33</sup>, the subsequent incorporation

of  $P^{33}$  into the peptide was quantified by Scintillation Proximity Assay (SPA - Amersham Pharmacia).

For IC<sub>50</sub> determination, test compounds were typically dissolved at 10mM in 100% DMSO, with subsequent serial dilution into 10% DMSO. Compounds were typically assayed  
5 over an eleven point dilution range with a concentration in the assay of 10uM to 3nM, in duplicate. IC<sub>50</sub> values were calculated by bespoke curve fitting software.

Assays were performed in clear bottomed, white walled, 96 well plates, in a total assay volume of 40ul. The assays contained: 1nM hROCK11; 1uM biotinylated peptide (biotin-Ahx-AKRRRLSSLRA-CONH<sub>2</sub>); 1uM ATP; 25Bq per pmole ATP<sup>33</sup>; 12.5mM Hepes  
10 pH7.4; 7.5mM MgCl<sub>2</sub>; 0.015% BSA. The reactions were incubated at 20°C for 120 minutes, then terminated by the addition of 10ul of 200mM EDTA.

Streptavidin PVT SPA beads were added to a concentration of 0.4mg per well. The plates were shaken for 10 minutes before centrifugation at 2500 rpm for 10 minutes.  $P^{33}$  incorporation was quantified by scintillation counting in a Wallac Trilux.

15

## 2. Aorta artery contraction assay:

Male Sprague-Dawley rats (350-400g) are anesthetized with 5% Isoflurane in O<sub>2</sub> and euthanized by exsanguination. Proximal descending thoracic aortae are removed and placed in oxygenated (95% O<sub>2</sub>, 5% CO<sub>2</sub>) ambient temperature Krebs solution (pH 7.4) with  
20 the following composition (mM): NaCl 112.0, KCl 4.7, CaCl<sub>2</sub> 2.5, KH<sub>2</sub>PO<sub>4</sub> 1.2, MgSO<sub>4</sub> 1.2, NaHCO<sub>3</sub> 25.0, dextrose 11.0, indomethacin 0.01, and L-NAME 0.1. The isolated aortae are cut into four 3mm rings and each segment is suspended by two 0.1mm diameter tungsten wire hooks and placed in a 10 mL organ bath containing oxygenated (95% O<sub>2</sub>, 5% CO<sub>2</sub>) 37°C Krebs solution (pH 7.4). The tissues are equilibrated under 1.0 grams resting tension  
25 for approximately 30 minutes. Responses are measured isometrically using a Grass FT 03 force-transducer and recorded on a Grass polygraph (model 7D) as change in tension.

After the equilibration period, each tissue is contracted with 60 mM KCl for about 15 minutes, washed with 37°C Krebs solution, and allowed to relax to the resting tension. The 60mM KCl contraction is repeated. The tissue is then contracted to equilibration with 1 M norepinephrine and washed with 37°C Krebs solution and allowed to relax to the resting  
5 tension.

A cumulative concentration-response curve to phenylephrine is obtained by dosing at 0.5 log unit intervals (1nM to 1 M) and the EC<sub>80</sub> is determined. Following several washes, each vessel is contracted to equilibrium with an EC<sub>80</sub> concentration of phenylephrine and tone is reversed by adding cumulative amounts of a ROCK inhibitor at 0.5 log unit intervals  
10 (0.1nM to 3 M). When constructing cumulative concentration-response, a higher concentration of vasoactive agent is added to the tissue bath after the previous response has reached a plateau.

### 3. In vivo effect of ROCK inhibitors (Intravenous, IV):

15 Rats are anaesthetised with isoflurane 3% for the implantation of femoral venous and arterial catheters. During the experiment, anaesthesia was maintained at 2%. Each rat received an intravenous bolus dose of vehicle followed by a bolus doses of ROCK inhibitors at 10, 30, 100 and 300 ug/kg with approx 20 minutes between doses. Blood samples are taken at 20 minutes after doses 10, 30 and 300 ug/kg for the subsequent determination of  
20 plasma levels of ROCK inhibitors.

Arterial blood pressure and heart rate derived from the blood pressure are recorded on strip chart and also on a computerised data acquisition system (Po-Ne-Mah, V 3.30, Gould Instruments). Hemodynamic data is presented as the maximum change from pre-dose control expressed as means +/- SEM.

25 The compounds of the invention are therefore useful in the treatment or prevention of diseases and/or conditions mediated through Rho kinases-1 and/or -2.

Thus the compounds are useful for the treatment or prophylaxis of

cardiovascular diseases such as hypertension, chronic and congestive heart failure, cardiac hypertrophy, restenosis, chronic renal failure and atherosclerosis. The compounds are useful for the treatment or prophylaxis of disorders associated with neuroinflammatory diseases such as stroke, spinal cord injury, multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and/or inflammatory disorders such as inflammatory pain, as rheumatoid arthritis, irritable bowel syndrome, inflammatory bowel disease.

The compounds are useful for the treatment or prophylaxis of asthma, female sexual dysfunction, male erectile dysfunctions and over-active bladder syndrome, cancer and tumor metastasis, viral and bacterial infections, insulin resistance and diabetes.

The invention therefore provides for the use of a compound of formula (I) and/or physiologically acceptable salts thereof for use in therapy and in particular for use as a medicine for inhibiting the effects of Rho kinases-1 and/or -2.

The invention also provides for the use of a compound of formula (I) and/or a physiologically acceptable derivative or salt thereof for the manufacture of a medicament for inhibiting the effects of Rho kinase-1/2.

The invention also provides for a method for inhibiting the effects of the Rho kinase-1/2 in a mammal e.g. a human, comprising administering to a patient in need thereof an effective amount of a compound of formula (I) and/or a physiologically acceptable derivative or salt thereof.

According to a further aspect, the invention also provides for a method for inhibiting the effects of the kinases Msk-1 and /or Rho kinase-1/2 in a mammal e.g. a human, comprising administering to a patient in need thereof an effective amount of a compound of formula (I) and/or a physiologically acceptable derivative or salt thereof.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established diseases or symptoms.

It will further be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated, the route of

administration and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician. In general however doses employed for adult human treatment will typically be in the range of 5 to 800mg per day, dependent upon the route of administration.

- 5 Preferred routes of administration include by intravenous injection or orally.

Thus for parenteral administration a daily dose regimen will typically be in the range 0.1 to 80mg/kg of the total body weight, preferably from about 0.2 to 30mg /kg or more preferably 0.5 to 15mg/kg.. For oral administration a daily dose regimen will typically be within the range range 0.1 to 80mg/kg of the total body weight, preferably from about 0.2 to

- 10 30mg /kg or more preferably 0.5 to 15mg/kg

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

- 15 While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

- The invention thus further provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers thereof and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.
- 20

- The compositions of the invention include those in a form especially formulated for oral, buccal, parenteral, inhalation or insufflation, implant or rectal administration. Appropriate dosage forms for administration by each of these routes may be prepared by conventional techniques.
- 25

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch or sodium starch glycollate, or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; solubilizers such as surfactants for example polysorbates or other agents such as cyclodextrins; and preservatives, for example, methyl or propyl p-hydroxybenzoates or ascorbic acid. The compositions may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The composition according to the invention may be formulated for parenteral administration by injection or continuous infusion. Formulations for injection may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively the active ingredient may be

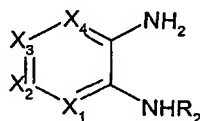


in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Conveniently the compounds of the invention are formulated for intravenous or oral administration.

- 5 The compositions according to the invention may contain between 0.1-99% of the active ingredient, conveniently from 30-95% for tablets and capsules and 3-50% for liquid preparations.

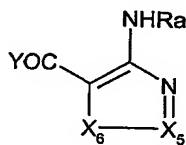
Compounds of formula (I) wherein  $R_1$  is a group (a), (c) and (d) may be prepared by reacting the diamine (II)



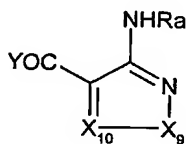
(II)

10

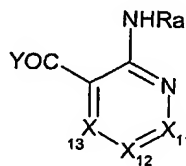
wherein  $R_2$ ,  $X_1$ ,  $X_2$ ,  $X_3$  and  $X_4$  have the meanings defined in (I) with the appropriate compound of formula (III), (IV) or (V)



(III)



(IV)



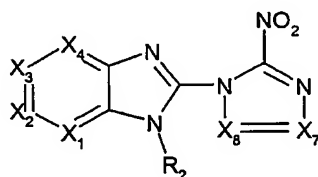
(V)

- 15 wherein Y is hydrogen, halogen e.g. Cl, Br or I, hydroxy or  $C_{1-4}$ alkoxy, Ra is hydrogen or a nitrogen protecting group such as an alkoxycarbonyl or benzyloxycarbonyl group and each of  $X_5$ ,  $X_6$ ,  $X_9$ ,  $X_{10}$ ,  $X_{11}$ ,  $X_{12}$  and  $X_{13}$  have the meanings as defined in formula (I) or is a group available thereto, followed when required by removal of the nitrogen protecting group Ra using conventional methods.

When Y is a group selected from halogen, alkoxy or hydroxy the reaction is carried out with heating and optionally in the presence of a solvent and/or a dehydrating agent such as polyphosphoric acid.

When Y is hydrogen the reaction is conveniently carried out in the presence of an oxidant such as sodium bisulphite.

Compounds of formula (I) wherein R<sub>1</sub> is the group (b) may be prepared by reduction of the corresponding nitro derivative (VI)

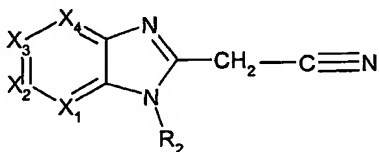


(VI)

wherein R<sub>2</sub>, R<sub>3</sub>, R<sub>3</sub>, X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, X<sub>7</sub> and X<sub>8</sub> have the meanings defined in formula (I).

The reduction may be effected using conventional procedures for converting a nitro group into an amino group, thus for example the reduction may be effected using hydrogen and a suitable metal catalyst e.g. palladium.

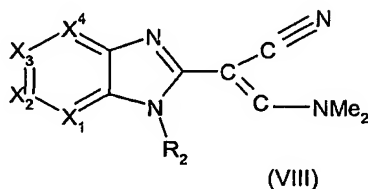
Compounds of formula (I) wherein R<sub>1</sub> is the group (c) and X<sub>9</sub> is oxygen and X<sub>10</sub> is nitrogen may be prepared by reacting the nitrile (VII)



(VII)

wherein R<sub>2</sub>, X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub> and X<sub>4</sub> have the meanings defined in formula (I) with hydrochloric acid and sodium nitrite in a solvent such as an alkanol and treatment of the product thus formed with a base e.g. aqueous sodium hydroxide and hydroxylamine and subsequent heating.

Compounds of formula (I) wherein  $R_1$  represent the group (c) wherein  $X_9$  is NH and  $X_{10}$  is CH may be prepared by reacting compound (VIII)



- 5 wherein  $R_2$ ,  $X_1$ ,  $X_2$ ,  $X_3$  and  $X_4$  have the meanings defined in formula (I) with hydrazine. This reaction is preferably carried out in a solvent e.g. an alkanol such as methanol and with heating.

In another aspect of the invention compounds of formula (I) may be converted into other compounds of formula (I).

- 10 Thus N-oxides of compounds of formula (I) may be prepared by treating a compound of formula (I) with a peroxy acid such as hydrogen peroxide in acetic acid.

For example reactions of a compound of formula (I) wherein  $X_2$  or  $X_3$  is N may be converted into the corresponding N-oxide i.e.  $X_2$  or  $X_3$  is N=O by reaction with hydrogen peroxide in acetic acid.

- 15 A compound of formula (I) wherein  $R_4$  or  $R_6$  is halogen e.g. chlorine or bromine may be prepared from the of formula (I) wherein  $X_2$  is N=O and  $X_1$  is CH or  $X_3$  is N=O and  $X_4$  is CH by reaction with the appropriate phosphorus oxyhalide e.g. phosphorus oxychloride or oxybromide.

- Compounds of formula (I) wherein  $R_6$  is alkoxy e.g. methoxy may be prepared by  
20 treating the corresponding compound wherein  $R_6$  is halogen e.g. chlorine or bromine with the appropriate alkanol e.g. methanol in the presence of a base such as sodium hydroxide.

Compounds of formula (I) wherein  $R_3$  or  $R_6$  is an optionally substituted aryl e.g. optionally substituted phenyl group or an optionally substituted heteroaryl group may be prepared by treating the corresponding compound wherein  $R_3$  and or  $R_6$  is halogen e.g.

chlorine or bromine by reaction with the corresponding optionally substituted aryl or heteroarylboronic acid in the presence of a suitable palladium catalyst  
e.g. bis(triphenylphosphine) palladium (II) dichloride or tetrakis (triphenylphosphine) palladium (0) or 1,1-bis (triphenylphosphono) ferrocene dichloropalladium (II) chloroform

- 5 complex and a base e.g. sodium carbonate. The reaction is preferably carried out in a solvent e.g. hydrocarbon such as toluene or ether such as 1,2-dimethoxyether or an amide such as DMF and with heating.

- Compounds of formula (I) wherein  $R_3$  is a group  $R_{19}S$  or  $R_{19}NH$  and wherein  $R_{19}$  is an optionally substituted aryl e.g. optionally substituted phenyl group or an optionally substituted heteroaryl group may be prepared by treating the corresponding compound wherein  $R_3$  is halogen e.g. bromine with the corresponding thiol  $R_{19}SH$  or amine  $R_{19}NH_2$  in the presence of a suitable palladium catalyst e.g. Tris(dibenzylidene-acetone)dipalladium and racemic-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl. The reaction is preferably carried out in a solvent e.g. an ether such as dioxane with heating.

- 15 Compounds of formula (I) wherein  $R_3$  is a group the group  $SO_2NR_{14}R_{15}$  may be prepared by treating the corresponding compound wherein  $R_3$  is halogen e.g. bromine with the sodium hydride and then n-butyllithium and the treating the resultant product sequentially with sulphur dioxide, sulphuryl chloride and then the amine  $HNR_{14}R_{15}$ . The reaction is conveniently carried out in a solvent such as tetrahydrofuran.

- 20 Compounds of formula (I) wherein  $R_6$  is an alkyl group e.g. methyl may be prepared by treating the corresponding compound wherein  $R_6$  is halogen e.g. bromine by reaction with the corresponding trialkylaluminium in the presence of bis(triphenylphosphine) palladium (II) dichloride. The reaction is preferably carried out in a solvent e.g. 1,4 dioxan and with heating.

- 25 Compounds of formula (I) in which  $R_2$  and/or  $R_3$  contain a phenyl group substituted by a methoxy group, as a substituent or part of a substituent may be converted into the

corresponding compound of formula (I) wherein the phenyl group is substituted by hydroxy, by reaction with boron tribromide in a suitable solvent such as dichloromethane.

Compounds of formula (I) wherein  $R_2$  is a phenyl group substituted by an optionally substituted alkoxy group e.g. a dialkylaminoalkoxy group may be prepared by reacting the  
5 corresponding compound of formula (I) wherein  $R_2$  is a phenyl group substituted by hydroxy with a suitable base e.g. sodium hydride in an aprotic solvent such as dimethylformamide and then the appropriate optionally substituted alkylhalide e.g. dialkylaminoalkylhalide.

Compounds of formula (I) wherein  $R_3$  is bromine may be converted into the corresponding wherein  $R_3$  is formyl by reaction with n-butyllithium and dimethylformamide in  
10 a solvent such as tetrahydrofuran followed by quenching with water.

Compounds of formula (I) wherein  $R_3$  is carboxyl may be prepared from the corresponding compound of formula (I) wherein  $R_3$  is bromine by reaction with lithium diisopropylamide and then butyl lithium in hexanes followed by treatment with carbon dioxide gas. The reaction is preferably carried out at a low temperature e.g.  $-78^\circ\text{C}$ .

15 Compounds of formula (I) wherein  $R_3$  is a methyl group substituted by a group selected from  $R_{19}\text{NH}$ ,  $R_{19}R_{20}\text{N}$ , or an N linked, 4-7 membered heterocyclic group (containing one or two hetero atoms selected from N, O or  $\text{S}(\text{O})_n$ ), may be prepared by reaction of the corresponding compound wherein  $R_3$  is formyl with the appropriate amine  $R_{19}\text{NH}_2$ ,  $R_{19}R_{20}\text{NH}$  or 4-7 membered heterocycle under reductive alkylation conditions. For  
20 example using a cyanoborohydride in a suitable solvent e.g. methanol. In this reaction if the groups  $R_{19}$ ,  $R_{20}$  or the 4-7 membered heterocycle contains an additional primary or secondary amino group then it is desirable to protect these using a conventional nitrogen protecting group such as a t-butyloxycarbonyl which may then be deprotected if so required.

Compounds of formula (I) wherein  $R_2$  or  $R_3$  is phenyl substituted by amino methyl  
25 and wherein the amino group refers to a group  $R_{19}\text{NH}$ ,  $R_{19}R_{20}\text{N}$  or an N linked 4-7 membered heterocyclic group containing one or two heteroatoms selected from N, O or  $\text{S}(\text{O})_n$  may be prepared by reacting the corresponding compound wherein  $R_2$  or  $R_3$  is phenyl substituted by

CHO under conventional reductive alkylation conditions such as those described above for preparing compounds wherein  $R_3$  is methyl substituted by  $R_{19}NH$  or  $R_{19}R_{20}N$ . The compounds of formula (I) wherein  $R_2$  is phenyl substituted by CHO may be prepared in situ from the corresponding compound wherein  $R_2$  is phenyl substituted by halogen e.g. bromine  
5 by reaction with n-butyllithium and dimethylformamide in a solvent such as tetrahydrofuran followed by quenching with water.

Compounds of formula (I) wherein  $R_3$  is the group  $CONR_{14}R_{15}$  and  $R_{14}$  and  $R_{15}$  have the meanings defined in formula (I) may be prepared from the corresponding compounds of formula (I) wherein  $R_3$  is carboxyl by reaction with the amine  $HNR_{14}R_{15}$  wherein  $R_{14}$  and  $R_{15}$   
10 have the meanings defined in formula (I) or are protected derivatives thereof under conventional procedures for preparing amides from acid followed by removal of the said protecting groups.

Conventionally the reaction is carried out by treating the acid with carbonyldimidiimidazole in a suitable solvent such as DMF followed by reaction with the amine  $HNR_{14}R_{15}$ .

15 Compounds of formula (I) wherein  $R_3$  is hydroxyl may be prepared from the corresponding compound wherein  $R_3$  is halogen e.g. bromine by reaction with n-butyl lithium in a solvent such as tetrahydrofuran or hexanes and tetrahydrofuran followed by addition of a trialkyl borate such as trimethylborate. The reaction is preferably carried out at low temperatures e.g.  $78^\circ C$  and then allowed to reach room temperature before being quenched  
20 by aqueous sodium hydroxide followed by aqueous hydrogen peroxide.

Compounds of formula (I) wherein  $R_3$  is the group  $R_{19}O$  and wherein  $R_{19}$  has the meaning defined in formula (I) hydroxyl may be prepared from the corresponding compound wherein  $R_3$  is hydroxyl by reaction with a group  $R_{19}La$  wherein  $R_{19}$  has the meaning defined in formula (I) is a protected derivative thereof and  $La$  is a leaving group. Thus  $La$  can be a  
25 halogen group e.g. bromines or iodine, or a hydroxyl which can be converted into a leaving group insitu e.g. by reaction with tributylphosphine and azodicarbonyl dipiperidine.

Compounds of formula (I) wherein  $R_3$  is an optionally substituted ethenyl grouping may be prepared by a compound of formula (I) wherein  $R_3$  is bromine by reaction with the appropriate ethene derivative in the presence of palladium acetate, or tolyltriphenylphosphine and a tertiary organic base such as triethylamine.

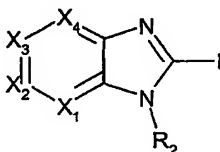
5        Compounds wherein  $R_3$  is an optionally substituted ethyl group may be prepared by treating the corresponding compound of formula (I) wherein  $R_3$  is halogen e.g. bromine by reaction with the corresponding optionally substituted ethenyl compound in the presence of 9-borobicyclo[3,3.1]-nonane and 1,1 bis(diphenylphosphono ferrocene dichloro palladium complex in a suitable solvent such as tetrahydrofuran and or dichloromethane.

10       In the above synthesis of compounds of formula (I) wherein they contain a primary or secondary amino grouping it may be necessary or desirable to carry out these procedures wherein the primary or secondary amine is in a protected form e.g. as a carbamate e.g. a t-butyl carbamate and then the carbamate converted into the required amine by conventional procedures, for example by the reaction with trifluoroacetic acid.

15       The nitrile of formula (VII) may be prepared by heating of a compound of formula (II) with ethyl cyanoacetate.

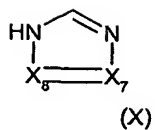
The compound of formula (VIII) may be prepared by reacting the nitrile of formula (VII) with an acetal of N, N dimethylformamide in a solvent e.g. a hydrocarbon such as ortho xylene and with heating.

20       Compounds of formula (VI) may be prepared by reaction of the 2-iodo-imidazole derivative (IX)



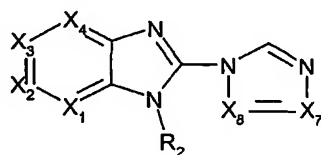
(IX)

wherein  $R_2$ ,  $X_1$ ,  $X_2$ ,  $X_3$  and  $X_4$  have the meanings defined in formula (I) with the compound (X)



wherein  $X_7$  and  $X_8$  have the meanings defined in formula (I)

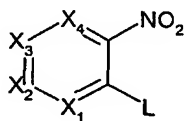
in the presence of a base and a polar aprotic solvent and then reacting the resultant compound (XI)



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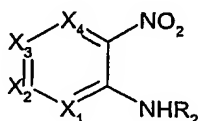
with an alkyl nitrite in the presence of a suitable base.

Compounds of formula (II) may be prepared by reacting a compound of formula (XII)



wherein  $X_1$ ,  $X_2$ ,  $X_3$  and  $X_4$  have the meanings defined above and L is a group displaceable by

10 the amine  $R_2NH_2$  e.g. methoxy, bromine, chlorine, fluorine or methoxysulphonyl to give the nitro amine (XIII)



followed by reduction of the nitro group by conventional means, for example using hydrogen and a palladium catalyst, iron and an organic acid e.g. acetic acid or with sodium dithionate.



When compounds of formula (I) contain an asymmetric centre the specific enantiomers arising there from may be obtained by conventional procedures. For example using preparative high performance liquid chromatography (HPLC) with a chiral stationary phase.

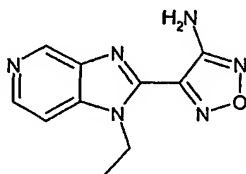
5            Physiologically acceptable acid addition salts of the compounds of formula (I) may be prepared by conventional procedures, for example by addition of a solution of the inorganic or organic acid in a suitable solvent e.g. an alkanol or an ether to a solution of the free base in a solvent such as an alkanol, e.g. methanol or an ether e.g. diethyl ether or tetrahydrofuran.

10           The compounds of formula (III), (IV), (V) (IX), (X) and (XII) are either known compounds or may be prepared by analogous methods to those preparing the known compounds.

The following examples are illustrative of the present invention and are not to be construed as a limitation of the scope of the invention.

15

**Example 1: 4-(1-Ethyl-1H-imidazo[4,5-c]pyridin-2-yl)furazan-3-ylamine**



**Step 1. Ethyl-(3-nitropyridin-4-yl)amine**

4-Methoxy-3-nitropyridine hydrochloride (11.2g, 58.9 mmol) in ethanol (75ml) was treated  
20    with a 70% solution of ethylamine in water (32ml) and heated under reflux for 1 hour. Further ethylamine solution (32ml) was added and the mixture heated under reflux for a further 2 hours. After cooling to room temperature, the solvent was removed *in vacuo* and the residue dissolved in ethyl acetate, washed (x3) with water and saturated aqueous sodium chloride

solution, dried over sodium sulphate and concentrated *in vacuo* to afford the title compound (8.7g, 88%); MS (ES+) m/e 168 [M+H]<sup>+</sup>.

**Step 2. *N*<sup>4</sup>-Ethylpyridine-3,4-diamine**

- 5 The product from Step 1 (8.7g, 52.0mmol) in ethanol (150ml) was hydrogenated for 18 hours in the presence of 10% palladium on carbon. After filtration of the catalyst through Kieselguhr, the filtrate was concentrated *in vacuo* to afford the title compound (6.7g, 94%); MS (ES+) m/e 138 [M+H]<sup>+</sup>.

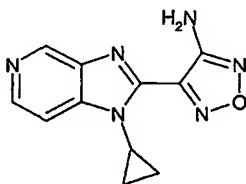
10 **Step 3. (1-Ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)acetonitrile**

The product from Step 2 (500mg, 3.6mmole) and ethyl cyanoacetate (620mg, 5.5mmol) were heated together at 190°C for 20 minutes. After cooling to room temperature, the residue was purified by column chromatography eluting with 10% methanol in ethyl acetate to afford the title compound (250mg, 37%); MS (ES+) m/e 187 [M+H]<sup>+</sup>.

15

**Step 4. 4-(1-Ethyl-1H-imidazo[4,5-c]pyridin-2-yl)furazan-3-ylamine**

The product from Step 3 (200mg, 1.1mmol) in methanol (4ml) and 2N hydrochloric acid (4ml) was treated portionwise with sodium nitrite (150mg, 2.2mmol) and stirred at room temperature for 2 hours. The pH of the mixture was adjusted to 12 by addition of 50% sodium hydroxide solution and a 50% solution of hydroxylamine in water (3ml) was added. The mixture was heated at 90°C for 2.5 hours and the reaction allowed to cool to room temperature. The resulting precipitate was filtered and dried *in vacuo* to afford the title compound (110mg, 43%); MS (ES+) m/e 231 [M+H]<sup>+</sup>.

**Example 2: 4-(1-Cyclopropyl-1H-imidazo[4,5-c]pyridin-2-yl)furazan-3-ylamine****Step 1. Cyclopropyl-(3-nitropyridin-4-yl)amine**

4-Methoxy-3-nitropyridine hydrochloride (2.0g, 11.3mmol) and cyclopropylamine (1.6ml, 22.6mmol) in ethanol (5ml) was treated with triethylamine (1.7ml, 12.4mmol) and heated under reflux for 18 hours. After cooling to room temperature, the solvent was removed *in vacuo* and the residue dissolved in dichloromethane, washed with water and saturated aqueous sodium chloride solution, dried over magnesium sulphate and concentrated *in vacuo* to afford the title compound (1.7g, 84%); MS (AP+) m/e 180 [M+H]<sup>+</sup>.

20

**Steps 2. 4-(1-Cyclopropyl-1H-imidazo[4,5-c]pyridin-2-yl)furazan-3-ylamine**

The title compound was prepared from the product of Step 1 using the methods of Example 1 Steps 2-4; MS (AP+) m/e 243 [M+H]<sup>+</sup>.

The following examples were prepared by the general two-step method described in Example 2.

	Example	Amine	Characterisation
3	4-(1-Methyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl)furazan-3-ylamine	Methylamine (8M in ethanol)	MS(AP+) m/e 217 [M+H] <sup>+</sup>
4	4-(1-Cyclohexyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl)furazan-3-ylamine	Cyclohexylamine	MS (ES+) m/e 285 [M+H] <sup>+</sup>
5	4-(1-Cyclopropylmethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl)furazan-3-ylamine	Cyclopropylmethylamine	MS(AP+) m/e 257 [M+H] <sup>+</sup>
6	4-(1-Cyclohexylmethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl)furazan-3-ylamine	Cyclohexylmethylamine	MS(AP+) m/e 299 [M+H] <sup>+</sup>
7	4-(1-Cyclobutyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl)furazan-3-ylamine	Cyclobutylamine	MS(AP+) m/e 257 [M+H] <sup>+</sup>
8	4-[1-(2-Ethylbutyl)-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl]furazan-3-ylamine	2-Ethyl- <i>N</i> -butylamine	MS(AP+) m/e 288 [M+H] <sup>+</sup>
9	4-(1-Isopropyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl)furazan-3-ylamine	Isopropylamine	MS(AP+) m/e 245 [M+H] <sup>+</sup>
10	4-(1- <i>sec</i> -Butyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl)furazan-3-ylamine	<i>sec</i> -Butylamine	MS(AP+) m/e 259 [M+H] <sup>+</sup>

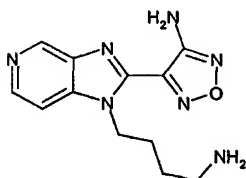
	ylamine		
11	4-(1-Cyclopentyl-1- <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl)-furazan-3-ylamine	Cyclopentylamine	MS(AP+) m/e 271 [M+H] <sup>+</sup>
12	4-(1-Cycloheptyl-1- <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl)-furazan-3-ylamine	Cycloheptylamine	MS(AP+) m/e 299 [M+H] <sup>+</sup>
13	4-[1-(2-Dimethylamino-1-methylethyl)-1- <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl]furazan-3-ylamine	<i>N</i> <sup>1</sup> , <i>N</i> <sup>1</sup> -Dimethyl-1,2-propanediamine	MS(AP+) m/e 288 [M+H] <sup>+</sup>
14	4-(1-Piperidin-4-yl)-1- <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl-furazan-3-ylamine	4-Amino-piperidine-1-carboxylic acid <i>tert</i> -butyl ester	MS(AP+) m/e 286 [M+H] <sup>+</sup>
15	4-[1-(4-Diethylamino-1-methylbutyl)-1- <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl]-furazan-3-ylamine	2-amino-5-diethylamino pentane	MS (AP+) m/e 344 [M+H] <sup>+</sup>
16	{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5- <i>c</i> ]pyridin-1-yl]-butyl}-carbamic acid <i>tert</i> -butyl ester	(4-Amino-butyl)-carbamic acid <i>tert</i> -butyl ester	MS (ES+) m/e 374 [M+H] <sup>+</sup>
17	4-[1-(3-Dimethylamino-propyl)-1- <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl]-	<i>N</i> <sup>1</sup> , <i>N</i> <sup>1</sup> -Dimethyl-propane-1,3-diamine	MS (ES+) m/e 288 [M+H] <sup>+</sup>

	furazan-3-ylamine	(Monatsh.Chem. <u>112</u> , 825-840 (1981))	
18	4-{1-[2-(4-Methyl-piperazin-1-yl)-ethyl]-1- <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl}-furazan-3-ylamine	2-(4-Methyl-piperazin-1-yl)-ethylamine (J.Med.Chem. <u>42</u> (15) 2870-2880 (1999))	MS (ES+) m/e 329 [M+H] <sup>+</sup> .

**Examples 19 and 20: (+)-4-[1-(2-Dimethylamino-1-methylethyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]furazan-3-ylamine and (-)-4-[1-(2-Dimethylamino-1-methylethyl)-1-*H*-Imidazo[4,5-*c*]pyridin-2-yl]furazan-3-ylamine**

5 The racemic product of Example 13 was separated into the title enantiomeric forms by preparative LC using Chiralcel OD, 10 micron particle size; 250 mm x 4.6 mm i.d.; n-Hexane : Ethanol, 99.7% v/v - 100% v/v ( 80:20 v/v ); 1.0 ml/min; UV detection at 215 nm yielding the (+) enantiomer [ $\alpha$ ]<sub>D</sub> + 6.8° ; HPLC t<sub>R</sub> 8.2min and the (-) enantiomer [ $\alpha$ ]<sub>D</sub> -2.2°; HPLC t<sub>R</sub> 9.0min.

10 **Example 21: 4-[1-(4-Amino-butyl)-1 *H* -imidazo[4,5- *c* ]pyridin-2-yl]-furazan-3-ylamine**



A solution of the product of Example 16 (155mg, 0.415mmol) in anhydrous dichloromethane (4ml) was treated with trifluoroacetic acid (4ml), and stirred at room temperature for 0.5 hours. The solvent was evaporated *in vacuo* and the residue partitioned between

15 dichloromethane and saturated sodium bicarbonate solution. The organic phase was washed with water (x3), and dried over anhydrous sodium sulphate, and the solvent evaporated *in vacuo*. The residue was purified by silica gel chromatography eluting with a

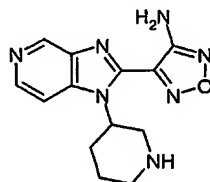
mixture of 0.880 ammonia:methanol:dichloromethane (1:9:90) to afford the title product (52mg, 46%). MS (ES+) m/e 274 [M+H]<sup>+</sup>.

The following compounds were prepared by the methods of Example 2 followed by the method of example 21:

	Example	Amine	Characterisation
22	4-(1-(1-Pyrrolidin-3-yl-1- <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl)-furazan-3-ylamine	3-amino-pyrrolidine-1-carboxylic acid <i>tert</i> -butyl ester (Syn. Comm. 2357-60 (1992))	MS (ES+) m/e 272 [M+H] <sup>+</sup> .
23	4-[1-(5-Amino-pentyl)-1- <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl]-furazan-3-ylamine	(5-Amino-pentyl)-carbamic acid <i>tert</i> -butyl ester (J. Med. Chem. <u>32</u> (2) 391-396 (1989))	MS (ES+) m/e 288 [M+H] <sup>+</sup> .
24	4-[1-(3-Amino-propyl)-1- <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl]-furazan-3-ylamine	(3-Amino-propyl)-carbamic acid <i>tert</i> -butyl ester (J. Org. Chem. <u>57</u> (21) 5687-5692 (1992))	MS (ES+) m/e 259 [M+H] <sup>+</sup> .

5

**Example 25. 4-(1-Piperidin-3-yl -1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine**



**Step 1. 3-(3-Nitro-pyridin-4-ylamino-piperidine-1-carboxylic acid *tert*-butyl ester.**

4-Chloro-3-nitropyridine (1.1g, 6.99mmol) in ethanol (12ml) was treated with 3-Amino-  
 10 piperidine-1-carboxylic acid *tert*-butyl ester (2.8g, 13.9mMol) followed by sodium acetate

(0.57g, 6.99mMol) and heated under reflux for 2 hours. After cooling to room temperature, the solvent was removed *in vacuo* and the residue dissolved in ethyl acetate, washed (x3) with water dried over magnesium sulphate and concentrated *in vacuo* to afford the title compound (2.1g, 94%); MS (ES+) *m/e* 323 [M+H]<sup>+</sup>.

5

**Step 2. 4-(1-Piperidin-3-yl -1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine**

The title compound was prepared from the product of step 1 using the method of example 1 Steps 2 to 4, then example 21. MS (ES+) *m/e* 286 [M+H]<sup>+</sup>.

The following compound was synthesised using the same 2-step procedure used to

10 make example 25.

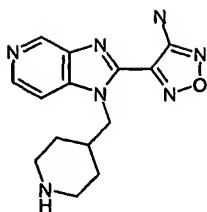
	Name	Amine	Data
26	4-[1-(2-Piperazin-1-yl-ethyl)-1- <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl]-furazan-3-ylamine	from 4-(2-Aminoethyl)-piperazine-1-carboxylic acid benzyl ester (J. Med. Chem. <u>30</u> (1) 121-131 (1987)	MS (ES+) <i>m/e</i> 315 [M+H] <sup>+</sup> .

**Examples 27 and 28: (+)-4-(1-Piperidin-3-yl -1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine and (-)-4-(1-Piperidin-3-yl -1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine**

The racemic product of Example 25 was separated into the title enantiomeric forms by preparative LC using Chiralpak AD, 10 micron particle size; 250 mm x 20 mm i.d.; n-Hexane : Ethanol, ( 50:50 v/v; pre-mixed); 17 ml/min; UV detection at 215 nm yielding the (+) enantiomer [α]<sub>D</sub> + 0.4° ; HPLC t<sub>R</sub> 6.6min and the (-) enantiomer [α]<sub>D</sub> -3.2°; HPLC t<sub>R</sub> 7.7min.

20 **Example 29. 4-(1-Piperidin-4-ylmethyl-1 *H*-imidazo (4,5-*c*)pyridin-2-yl)-furazan-3-ylamine**





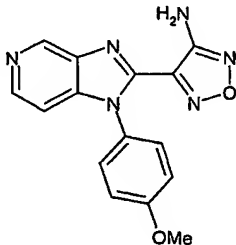
**Step 1. 4-((3-Nitro-pyridin-4-ylamino)-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester.**

4-Methoxy-3-nitropyridine hydrochloride (2.26g, 11.9mmol) in ethanol (15ml) was treated  
 5 with 4-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (3.05g, 14.2mMol) followed  
 by triethylamine (1.82ml, 13.1mMol) and heated under reflux for 6 hours. After cooling to  
 room temperature, the solvent was removed *in vacuo* and the residue dissolved in ethyl  
 acetate, washed (x3) with water, brine, dried over sodium sulphate and concentrated *in*  
*vacuo* to afford the title compound (2.78g, 77%); <sup>1</sup>H NMR (400MHz) δ9.21 (1H (s) Ar-H),  
 10 δ8.30(1H,(d) Ar-H), δ 8.2 (1H, (s) N-H) δ6.70 (1H, (d) Ar-H), δ4.04 (2H (broad), CH<sub>2</sub>) δ3.25  
 (2H, (t) piperidine) δ2.73 (2H, (broad) piperidine), δ 1.79 (1H, (broad) piperidine), δ1.46 (9H,  
 (s) <sup>t</sup>Bu).

**Steps 2. 4-(1-Piperidin-4-ylmethyl-1 *H*-imidazo (4,5-*c*)pyridin-2-yl)-furazan-3-ylamine**

15 The title compound was prepared from the product of step 1 according to the method of  
 example 1 steps 2-4, followed by the method of example 21. MS (ES<sup>+</sup>) *m/e* 300 [M+H]<sup>+</sup>.

**Example 30: 4-[1-(4-Methoxy-phenyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-furazan-3-ylamine**



20 **Step 1: (4-Methoxy-phenyl)-(3-nitro-pyridin-4-yl)-amine**

To a solution of 4-chloro-3-nitropyridine (Kruger J, Mann F.G, *J. Chem. Soc.*, 1955, 2755) (700mg, 4.41mmol) in ethanol (10ml) was added 4-methoxyaniline (1.087g, 8.82mmol), followed by sodium acetate (362mg, 4.41mmol). The mixture was heated under reflux for 16 hours, cooled to room temperature and diluted with water (30ml). The resulting precipitate  
 5 was collected by filtration, washed with water (x3) and dried *in vacuo* to afford the title compound (800mg, 74%); MS (ES+) m/e 309 [M+H]<sup>+</sup>.

**Step 2: 4-[1-(4-Methoxy-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine**

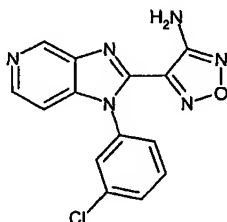
The title compound was prepared from the product of Step 1 using the methods of Example  
 10 1 Steps 2-4; MS (AP+) m/e 309 [M+H]<sup>+</sup>.

The following examples were prepared by the general two-step method described in Example 30.

	Example	Aniline	Characterisation
31	4-(1-Phenyl-1 H -imidazo[4,5- c ]pyridin-2-yl)-furazan-3-ylamine	Aniline	MS (ES+) m/e 279 [M+H] <sup>+</sup>
32	4-[1-(4-Amino-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	4-amino acetanilide	MS (ES+) m/e 294 [M+H] <sup>+</sup>
33	4-[1-(3-Methoxy-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	3-methoxy aniline	MS (ES+) m/e 309 [M+H] <sup>+</sup>
34	4-[1-(2-Methoxy-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	2-methoxy aniline	MS (ES+) m/e 309 [M+H] <sup>+</sup>

35	4-[1-(2-Ethyl-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	2-ethyl aniline	MS (ES+) m/e 307 [M+H] <sup>+</sup>
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**Example 36: 4-[1-(3-Chloro-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine**



5

**Step 1: (3-Chloro-phenyl)-(3-nitro-pyridin-4-yl)-amine**

The title compound was prepared from 3-chloro aniline using the procedures detailed in Example 30 Step 1.

10 **Step 2: N4-(3-Chloro-phenyl)-pyridine-3,4-diamine**

The product of Step 1 (325mg, 1.302mmol), was dissolved in ethanol (20ml), and treated with iron powder (727mg, 13.017mmol), 20 drops of 37% hydrochloric acid and water (2ml), and refluxed for 1 hour. The reaction was then filtered hot, and the filtrate evaporated *in vacuo*. The residue was dissolved in ethyl acetate then washed with saturated sodium bicarbonate solution, water, and brine, separated, dried over anhydrous sodium sulfate and evaporated *in vacuo* to afford the title compound (253mg, 88%). MS (ES+), m/e 220/222 [M+H]<sup>+</sup>.

15

**Step 3: 4-[1-(3-Chloro-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine**

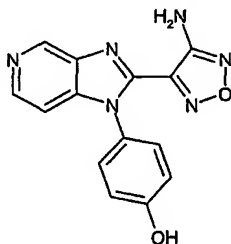
The title product was prepared using the general method described in Example 1 Step 3-4;

MS (ES+), m/e 313/315 [M+H]<sup>+</sup>.

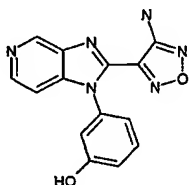
The following example was prepared by the general 3 step method described in example 36.

37	4-[1-(3-bromo-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	3-bromo aniline	MS (ES+) m/e 357/359 [M+H] <sup>+</sup>
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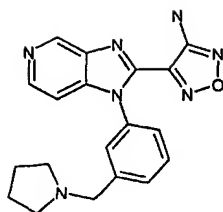
**Example 38: 4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenol**

To a solution of the product of Example 30 (100mg, 0.32mmol) in anhydrous dichloromethane (10ml) stirred at 0°C, was added dropwise a 1.0M solution of boron tribromide (2.91ml, 2.92mmol) in dichloromethane and the mixture stirred at room temperature for 16 hours. The reaction was then quenched with water (20ml), and the pH adjusted to 14 with 50% sodium hydroxide solution. The aqueous phase was washed with dichloromethane (x3), neutralised with 5N hydrochloric acid, and the resulting precipitate collected, washed with water (x3), diethyl ether and dried *in vacuo* to yield the title compound (59mg, 62%); MS (ES+) m/e 295 [M+H]<sup>+</sup>.

**Example 39: 3-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenol**

The title compound was prepared from the product of Example 33 using the procedure detailed in Example 38.

**Example 40: 4-[1-(3-Pyrrolidin-1-ylmethyl-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine**



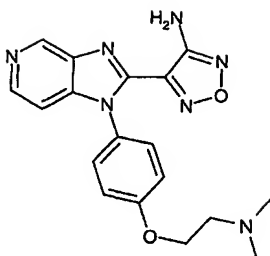
**Step 1 : 3-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-benzaldehyde**

The product of Example 37 (1.07g, 3mmol) in anhydrous tetrahydrofuran at  $-78^{\circ}\text{C}$  was treated dropwise with a 2.5M solution of n-butyllithium (3.6ml, 9mmol) in hexanes, followed by anhydrous dimethylformamide (10ml) and stirred for 10 minutes. The reaction was then warmed to room temperature, quenched with water and extracted with dichloromethane (X3). The combined organic phase was washed with water, brine, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was purified using silica gel chromatography, eluting with a mixture of ethyl acetate / pentane (3:1) to afford the title compound (75mg, 8%); MS (ES<sup>+</sup>), m/e 307 [M+H]<sup>+</sup>.

**Step 2: 4-[1-(3-Pyrrolidin-1-ylmethyl-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furan-3-ylamine**

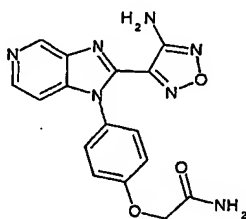
The product of Step 1 was stirred in 1,2-dichloroethane, and treated with pyrrolidine (27uL, 0.326mmol) and stirred for 15 minutes at room temperature. The reaction was then treated with sodium triacetoxyborohydride (34mg, 0.164mmol) and stirred at room temperature for 16 hours. The reaction was diluted with methanol and applied to a Mega Bond Elute SCX ion exchange column, eluting sequentially with water, methanol and finally 0.880 ammonia:methanol (1:9). The residue was purified using silica gel chromatography eluting with a mixture of 0.880 ammonia:methanol:dichloromethane (1:9:90) to afford the compound (20mg, 34%); MS (ES<sup>+</sup>), m/e 362 [M+H]<sup>+</sup>.

**Example 41: 4-[1-[4-(2-Dimethylamino-ethoxy)-phenyl]-1 H -imidazo[4,5- c ]pyridin-2-yl]-furan-3-ylamine hydrochloride**



To a solution of the product of Example 38 (30mg, 0.102mmol), in *N,N*-dimethylformamide (2ml), was added sodium hydride (60% dispersion in mineral oil, 4mg, 0.10mmol). After 5 minutes at room temperature 2-(dimethylamino)ethyl chloride hydrochloride (15mg, 0.102mmol) and sodium hydride (60% dispersion in mineral oil, 4mg, 0.102mmol) were added and the reaction heated at 60°C for 5 hours. The solvent was evaporated *in vacuo* and the residue was partitioned between ethyl acetate and 2M sodium hydroxide solution. The organic phase was separated then washed with water (x3), dried over anhydrous sodium sulphate and evaporated *in vacuo*. Purification of the residue by silica gel chromatography eluting with 10% methanol in dichloromethane gave the free base of the title compound. The product was dissolved in methanol (1ml) and treated with a 1M solution hydrochloric acid (36uL, 0.036mmol) in diethyl ether and evaporated *in vacuo* to yield the title compound (14mg, 32%); MS (ES+) *m/e* 366 [M+H]<sup>+</sup>.

**Example 42: 2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-*c*]pyridin-1-yl]-phenoxy}-acetamide trifluoroacetate**



The product of Example 38 (77.0mg, 0.0260mmol) was dissolved in *N,N*-dimethylformamide (1.5 ml) and sodium hydride (60% dispersion in oil, 11.5 mg, 0.286mmol) was added (gas

evolution!). After 5 minutes at room temperature, chloroacetamide (36.5mg, 0.390mmol) was added and the solution was heated to 60°C for 3 hours. The reaction mixture was partitioned between ethyl acetate and satd. aqueous NaHCO<sub>3</sub>. The aqueous phase was washed with EtOAc (x2), dried over anhydrous sodium sulfate and evaporated *in vacuo*.

- 5 Purification of the residue by preparative HPLC (0-80% CH<sub>3</sub>CN/H<sub>2</sub>O (0.1% TFA), retention time = 5.35 minutes) afforded the title compound as a white solid (58 mg, 48%). MS (ES+) m/e 352 [M+H]<sup>+</sup>.

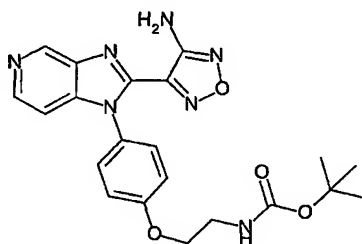
The following examples were prepared by the general method described in Example 42.



	Example	Alkyl Halide	Characterisation
43	2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-N,N-dimethylacetamide	N,N-dimethyl chloroacetamide	MS(ES+) m/e 366 [M+H] <sup>+</sup>
44	2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-ethanol	2-bromoethanol	MS(ES+) m/e 339 [M+H] <sup>+</sup>
45	3-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-propionitrile	3-chloropropionitrile	MS(ES+) m/e 429 [M+H] <sup>+</sup>
46	3-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-propan-1-ol	3-bromopropanol	MS(ES+) m/e 353 [M+H] <sup>+</sup>
47	2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-N-methylacetamide	N-Methyl chloroacetamide	MS(ES+) m/e 366 [M+H] <sup>+</sup>
48	4-[1-(4-Methylsulfanyl-methoxyphenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	Chloromethyl methyl sulfide	MS(ES+) m/e 355 [M+H] <sup>+</sup>

49	4-[1-(4-Phenylsulfanyl-methoxy-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furan-3-ylamine	Chloromethyl phenyl sulfide	MS(ES+) m/e 433 [M+H] <sup>+</sup>

**Example 50: (2-{4-[2-(4-Amino-furan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-ethyl)-carbamic acid *tert*-butyl ester trifluoroacetate**



- 5 To a suspension of the product of Example 38 (0.400g, 1.36 mmol) in 1,4-dioxane was added triphenylphosphine (534mg, 2.04 mmol) and *N*-BOC ethanolamine (0.316mL, 2.04mmol). Diisopropylazodicarboxylate (0.401 mL, 2.04mmol) was added. After 14.5 hours, the reaction mixture was evaporated *in vacuo*. The resulting residue was purified by preparative HPLC (0-80% CH<sub>3</sub>CN/H<sub>2</sub>O (0.1% TFA), retention time = 7.75 minutes) affording
- 10 the title compound as the trifluoroacetate salt (383 mg, 51%). MS (ES+) m/e 438 [M+H]<sup>+</sup>.

The following example was prepared according to the general procedure described in Example 50:

	Example	Alcohol	Characterisation
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51	4-{1-[4-(2-Methylamino-ethoxy)-phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine	N-methyl ethanolamine	MS(ES+) m/e 352 [M+H] <sup>+</sup>
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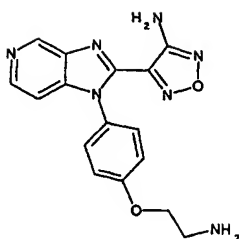
**Examples 52 and 53: 4-[1-(4-Benzenesulfinylmethoxy-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine and 4-[1-(4-Benzenesulfonylmethoxy-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine**

- 5           The product of Example 49 (28.0mg, 0.053mmol) was dissolved in methanol (0.600mL) and H<sub>2</sub>O(0.300mL). Sodium periodate (14 mg, 0.065mmol) was added and the reaction was allowed to stir for four days. The solution was partitioned between ethyl acetate and aq. NaCl. The organic phase was dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by preparative HPLC (0-80% CH<sub>3</sub>CN/H<sub>2</sub>O
- 10 (0.1% TFA) sulfoxide retention time = 6.79 minutes; sulfone = 7.45 minutes) to yield the title compounds as their trifluoroacetate salts: Example 52 (sulfoxide) (10.0 mg, 35%), MS (ES+) m/e 433 [M+H]<sup>+</sup>; Example 53 (sulfone) (3.2mg, 11%), MS (ES+) m/e 449 [M+H]<sup>+</sup>

**Example 54: 4-[1-(4-Methanesulfinylmethoxy-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine**

The title compound was prepared from the product of example 48 according to the procedure described for example 52. MS (ES+) m/e 371 [M+H]<sup>+</sup>

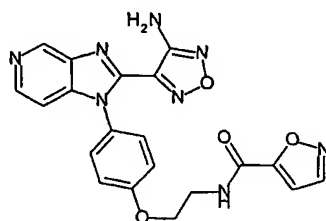
**Example 55: 4-[1-[4-(2-Amino-ethoxy)-phenyl]-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine hydrochloride**



The product of Example 50 was treated with 4.0 M HCl/dioxane. After two hours, the reaction was judged complete by LC-MS. The reaction mixture was concentrated *in vacuo* to provide the title compound as a white powder (245mg, 86%). MS(ES<sup>+</sup>) m/e 339 [M+H]<sup>+</sup>

5

**Example 56: Isoxazole-5-carboxylic acid (2-{4-[2-(4-amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-ethyl)- amide**



The product of example 55 was suspended in dichloromethane (0.5mL) and triethylamine (0.025 mL, 0.173mmol) was added. Isoxazole 5-carboxylic acid (0.010mL, 0.073mmol) was added. After 2.5 hours, the reaction mixture was partitioned between ethyl acetate and 2N NaOH. The aqueous phase was washed with ethyl acetate (x1). The combined organic phases were washed with satd. aq. NaCl, dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by preparative HPLC (0-80% CH<sub>3</sub>CN/H<sub>2</sub>O (0.1% TFA), retention time = 6.42 minutes) to yield the title compound as the trifluoroacetate salt (7.0 mg, 26%). MS (ES<sup>+</sup>) m/e 433 [M+H]<sup>+</sup>.

15

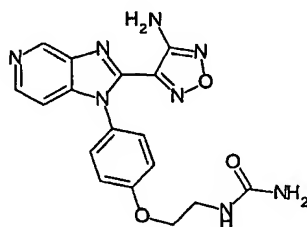
The following example was prepared according to the general procedure described in Example 56:

	Example	Acid Chloride	Characterisation
57	<i>N</i> -(2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5- <i>c</i> ]pyridin-1-yl]-phenoxy}-ethyl)-acetamide	Acetyl chloride	MS(ES+) m/e 380 [M+H] <sup>+</sup>

The following example was prepared according to the general procedure described in Example 56, using an additional equivalent of triethylamine:

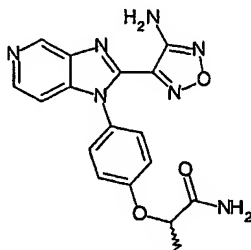
58	<i>N</i> -(2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5- <i>c</i> ]pyridin-1-yl]-phenoxy}-ethyl)-isonicotinamide	isonicotinoyl chloride hydrochloride	MS(ES+) m/e 433 [M+H] <sup>+</sup>
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5 **Example 59: (2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-*c*]pyridin-1-yl]-phenoxy}-ethyl)-urea**



The product of example 55 (25mg, 0.061 mmol) was dissolved in THF (0.350 mL) and H<sub>2</sub>O (0.150 mL). A solution of KOCN (25mg, 0.0608mmol) in H<sub>2</sub>O (0.150 mL) was added to the reaction slowly dropwise over 30 minutes. After an additional 1.5 hours, the reaction was judged complete by LC-MS analysis. The reaction mixture was partitioned between EtOAc and dilute aq. NaHCO<sub>3</sub>. The aqueous phase was washed with EtOAc (x1) and the combined organic phases were dried over sodium sulfate, filtered, and concentrated. Trituration with diethyl ether provided a white solid (5.0mg, 22%). MS(ES+) m/e 381 [M+H]<sup>+</sup>

**Example 60: 2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-propionamide**



**Step 1. 2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-propionic acid methyl ester**

The ester was prepared from the product of Example 38 (58.0 mg) as described in Example 42, employing methyl 2-bromopropionate as the alkyl halide. The ester was used directly in Step 2. MS(ES+) m/e 381 [M+H]<sup>+</sup>

10

**Step 2. 2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-propionamide**

The product of Step 1 was dissolved in methanol (1.0 mL) and concentrated ammonium hydroxide (0.500 mL) was added. After 14.5 hours, a white precipitate was evident. The

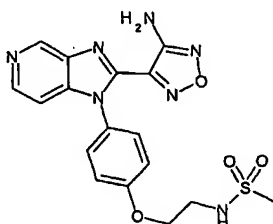
15 reaction mixture was filtered and the solid washed with water and diethyl ether. The title compound was isolated as an off-white powder (12.5 mg, 20%). MS(ES+) m/e 366 [M+H]<sup>+</sup>

The following example was prepared according to the procedure described in Example 60, Steps 1 and 2.

	Example	Alkyl Halide	
61	2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-2-methyl-	Ethyl 2-bromoisobutyrate	MS(ES+) m/e 366 [M+H] <sup>+</sup>

	propionamide		
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**Example 62: N-(2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-ethyl)-methanesulfonamide**



**5 Step 1. 4-{1-[4-(2-Bromo-ethoxy)-phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine trifluoroacetate**

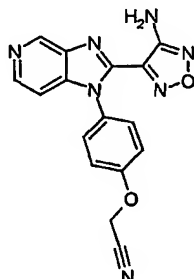
The title compound was prepared using the procedure described in example 50, using 2-bromoethanol as the alcohol. MS(ES<sup>+</sup>) m/e 381 [M+H]<sup>+</sup>

**10 Step 2. N-(2-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-ethyl)-methanesulfonamide**

The product of Step 1 (21.5mg, 0.042mmol) and methanesulfonamide (8.0mg, 0.080mmol) were dissolved in DMF. Sodium hydride (60% dispersion in mineral oil, 5.3mg, 0.133mmol) was added to the reaction, and the mixture was heated to 60 °C. After two hours, the  
 15 reaction was judged complete by LC-MS. The reaction mixture was poured into EtOAc and diluted with pH 7 phosphate buffer.

The layers were separated and the aqueous layer washed with EtOAc (x3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The resulting residue was purified by preparative HPLC (0-80% CH<sub>3</sub>CN/H<sub>2</sub>O (0.1% TFA),  
 20 retention time = 6.29 minutes) to yield the title compound as the trifluoroacetate salt (5.0 mg, 22%). MS (ES<sup>+</sup>) m/e 416 [M+H]<sup>+</sup>.

**Example 63: {4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenoxy}-acetonitrile**



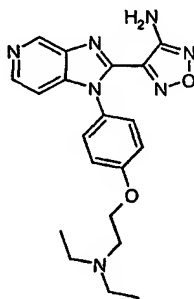
- 5 To a solution containing 150 mg of the product from Example 38 (0.51 mmols) in 2.6 mL of dry DMF was added 25 mg of NaH (0.61 mmols, 60% suspension in oil). After stirring at ambient temperature for 5 min, 0.033 mL of chloroacetonitrile (0.51 mmols) was added to the reaction via syringe. The reaction was warmed to 60°C for 16 h. After cooling to room temperature, 1 mL of water was carefully added to the reaction mixture. The mixture was
- 10 diluted with 20 mL of EtOAc and washed with 2N NaOH (3 X 10 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. The residue was dissolved in a minimum volume of DMSO and filtered through a 0.45 μm acrodisc filter. The resulting solution was purified on the Gilson reverse-phase HPLC to afford the title product (4 mg, 2%). MS (ES<sup>+</sup>) m/e 334 [M+H]<sup>+</sup>.
- 15 The following examples were prepared using the general method of Example 63.

	Example	alkyl halide or alkyl mesylate	Characterization
64	4-{1-[4-(2-Dimethylamino-1-methylethoxy)-phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-	(2-chloro-propyl)-dimethyl-amine	MS (ES <sup>+</sup> ) m/e 380 [M+H] <sup>+</sup>



	furazan-3-ylamine		
65	4-{1-[4-((S)-1-Methyl-pyrrolidin-2-ylmethoxy)-phenyl]-1 H -imidazo[4,5- c ]pyridin-2-yl}-furazan-3-yl amine	((S)-1-Methyl-pyrrolidin-2-yl)-methyl-mesylate	MS (ES <sup>+</sup> ) m/e 392 [M+H] <sup>+</sup>
66	4-(1-[4-[2-(Benzyl-methyl-amino)-ethoxy]-phenyl]-1 H -imidazo[4,5- c ]pyridin-2-yl)-furazan-3-ylamine	N-(2-chloroethyl)-N-methylbenzylamine hydrochloride	MS (ES <sup>+</sup> ) m/e 442 [M+H] <sup>+</sup>

**Example 67: 4-{1-[4-(2-Diethylamino-ethoxy)-phenyl]-1 H -imidazo[4,5- c ]pyridin-2-yl}-furazan-3-ylamine**



- 5 To a solution containing 50 mg the product from Example 38 (0.17 mmols) in 3.4 mL of dry DMF was added 14 mg of NaH (0.34 mmols, 60% suspension in oil). After stirring at ambient temperature for 5 min, 44 mg of 2-bromoethyl-diethylamine (0.17 mmols) was added to the reaction. The reaction was warmed to 60°C for 16 h. After cooling to room temperature, 1 mL of water was carefully added to the reaction mixture. The mixture was

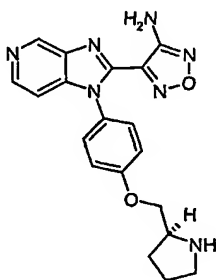
- diluted with 20 mL of EtOAc and washed with 2N NaOH (3 X 10 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. The residue was dissolved in a minimum volume of DMSO and filtered through a 0.45  $\mu$ m acrodisc filter. The resulting solution was purified on the Gilson reverse-phase HPLC. The resulting product was
- 5 dissolved in a minimum amount of MeOH and treated with excess 1N HCl in diethylether. The resulting precipitate was collected and washed with diethylether to afford the title product (11 mg, 17%). MS (ES<sup>+</sup>) m/e 393 [M]<sup>+</sup>.

The following examples were prepared using the same general method for Example 67.

	Example	alkyl halide	Characterization
68	4-{1-[4-(3-Dimethyl amino-propoxy)-phenyl]-1 H -imidazo[4,5- c]pyridin-2-yl}-furan-3-ylamine	N-(3-chloropropyl)-dimethylamine	MS (ES <sup>+</sup> ) m/e 380 [M+H] <sup>+</sup>
69	4-{1-[4-(3-Diisopropylamino-ethoxy)-phenyl]-1 H -imidazo[4,5- c]pyridin-2-yl}-furan-3-ylamine	N-(2-chloroethyl)-diisopropyl-amine hydrochloride	MS (ES <sup>+</sup> ) m/e 422 [M+H] <sup>+</sup>
70	4-{1-[4-(3-Morpholin-4-yl-ethoxy)-phenyl]-1 H -imidazo[4,5- c	N-(2-chloroethyl)-morpholine	MS (ES <sup>+</sup> ) m/e 408 [M+H] <sup>+</sup>

	]pyridin-2-yl)- furazan-3-ylamine		
71	4-{1-[4-(1-Methyl- piperidin-4-yloxy)- phenyl]-1 H - imidazo[4,5- c ]pyridin-2-yl)- furazan-3-ylamine	N-methyl-4-chloro- piperidine hydrochloride	MS (ES <sup>+</sup> ) m/e 392 [M+H] <sup>+</sup>
72	4-{1-[4-(2-Piperidin - 1-yl-ethoxy)- phenyl]-1 H - imidazo[4,5- c ]pyridin-2-yl)- furazan-3-ylamine	N-(2-chloroethyl)- piperidine hydrochloride	MS (ES <sup>+</sup> ) m/e 406 [M+H] <sup>+</sup>

**Example 73: 4-{1-[4-((S)-1-Pyrrolidin-2-ylmethoxy)-phenyl]-1 H -imidazo[4,5- c ]pyridin-2-yl}-furazan-3-ylamine**

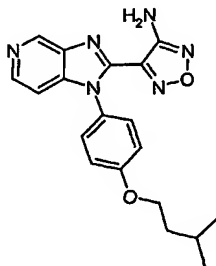


- 5 This example was prepared using the same general method of Example 67 using (S)-(-)-1-(*tert*-butoxycarbonyl)-2-pyrrolidinemethyl-mesylate (48 mg, 23%). MS (ES<sup>+</sup>) m/e 378 [M+H]<sup>+</sup>

The following examples were prepared from the product of Example 38 using the general method of Example 39

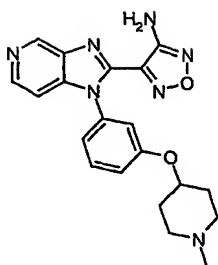
	Example	Alkyl halide	Characterization
74	4-{1-[3-(2-Dimethyl amino-ethoxy)-phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine	N-(2-chloro-ethyl)-dimethyl-amine hydrochloride	MS (ES <sup>+</sup> ) m/e 366 [M+H] <sup>+</sup>
75	4-{1-[3-(3-Dimethylamino-propoxy)-phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine	N-(2-chloro-propyl)-dimethyl-amine hydrochloride	MS (ES <sup>+</sup> ) m/e 380 [M+H] <sup>+</sup>

**Example 76: 4-{1-[4-(3-Methyl-butoxy)-phenyl]-1 H -imidazo[4,5- c ]pyridin-2-yl}-furazan-3-ylamine**



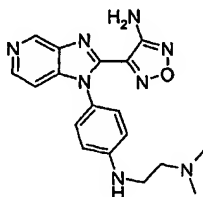
5 The title compound was prepared using the same general method for Example 50 starting from isoamyl alcohol. MS (ES<sup>+</sup>) m/e 364 [M+H]<sup>+</sup>

**Example 77: 4-{1-[3-(1-Methyl-piperidin-4-yloxy)-phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine**



The title compound was prepared from the product of Example 39 using the general method of Example 50 using N-methyl-4-hydroxy-piperidine. MS (ES<sup>+</sup>) m/e 392 [M+H]<sup>+</sup>

- 5 **Example 78: N-(4-[2-(4-Amino-furazan-3-yl)-1H-imidazo[4,5-c]pyridin-2-yl]-phenyl)-N', N'-dimethyl-ethane-1,2-diamine**



**Step 1. 4-[1-(4-Amino-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine**

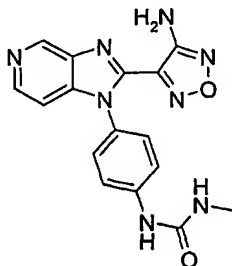
- 10 The title compound was prepared by the method of Example 25 starting from 4-chloro-3-nitro pyridine and (4-aminophenyl)-carbamic acid t-butyl ester. MS (ES<sup>+</sup>) m/e 294 [M+H]<sup>+</sup>

**Step 2. N-(4-[2-(4-Amino-furazan-3-yl)-1H-imidazo[4,5-c]pyridin-1-yl]-phenyl)-N', N'-dimethyl-ethane-1,2-diamine**

- 15 To a solution containing 500 mg the product from Step 1 (1.7 mmol) in 10 mL DMF was added 200 mg of NaH (60% dispersion in oil, 5.1 mmol). After 2 hours at room temperature, 246 mg of 2-(dimethylamino)ethyl chloride hydrochloride (1.7 mmol) was added, and the reaction mixture was heated to 60 °C for 5 hours. The solvent was evaporated *in vacuo* to yield a residue which was partitioned between ethyl acetate and brine. The organic phase

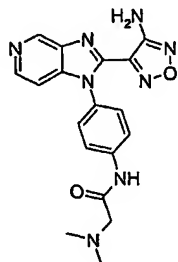
was dried over anhydrous sodium sulphate, filtered, and concentrated *in vacuo*. Purification of the residue by Gilson reverse-phase HPLC afforded the title compound (24 mg, 4 %). MS (ES<sup>+</sup>) m/e 365 [M+H]<sup>+</sup>

**Example 79: 1-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenyl}-3-methyl-urea**



To a solution containing 50 mg the product from Example 78, Step 1 (0.17 mmol) in 1 mL pyridine, was added 20 mg of methyl isocyanate (0.34 mmol) dropwise at 0 °C. The resulting mixture was stirred at room temperature for 5 hours. The solvent was evaporated *in vacuo* to yield a residue which was partitioned between ethyl acetate and brine. The organic phase was dried over anhydrous sodium sulphate, filtered, and concentrated *in vacuo*. Purification of the residue by Gilson reverse-phase HPLC afforded the title compound (5.4 mg, 9.0 %). MS (ES<sup>+</sup>) m/e 351 [M+H]<sup>+</sup>

**Example 80: N-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenyl}-C-dimethylamino-acetamide**



To a solution containing 100 mg of the product of Example 78, Step 1 (0.3 mmol) in 5 mL  $\text{CH}_2\text{Cl}_2$ , was added 65 mg of dimethylamino acetyl chloride (0.4 mmol) and 92mg of triethylamine (0.9 mmol). The resulting mixture was heated to reflux for 12 hours. The reaction was cooled to ambient temperature and the solvent was concentrated *in vacuo*.

- 5 The resulting residue was partitioned between ethyl acetate and brine. The organic phase was dried over anhydrous sodium sulphate, filtered, and concentrated *in vacuo*. Purification of the residue by Gilson reverse-phase HPLC afforded the title compound (38 mg, 30%). MS ( $\text{ES}^+$ ) m/e 379  $[\text{M}+\text{H}]^+$

The following examples were prepared using the general method of Example 30

	Example	Aniline	Characterization
81	4-[1-(1H-Indazol-5-yl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	5-amino-indazole	MS ( $\text{ES}^+$ ) m/e 319 $[\text{M}+\text{H}]^+$
82	4-[1-(1H-Indazol-6-yl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	6-amino-indazole	MS ( $\text{ES}^+$ ) m/e 319 $[\text{M}+\text{H}]^+$
83	4-[1-[4-(3-Dimethylamino-propyl)-phenyl]-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	4-(3-dimethylamino propyl)aniline (Klein, C. D. P.; Klingmueller, M.; Schellinski, C.; Landmann, S.; Hauschild, S.; Heber,	MS ( $\text{ES}^+$ ) m/e 364 $[\text{M}+\text{H}]^+$

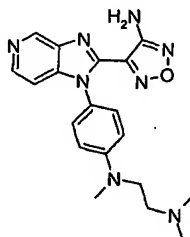
		D.; Mohr, K.; Hopfinger, A. J. <i>J. Med. Chem.</i> <b>1999</b> , 42, 3874 - 3888.	
84	4-[1-(4-Dimethylamino-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furan-3-ylamine	<i>N,N</i> -Dimethyl-benzene-1,4-diamine (Wurster; <i>Chem. Ber.</i> <b>1879</b> , 12, 523.)	MS (ES <sup>+</sup> ) m/e 322 [M+H] <sup>+</sup>
85	4-(1-enzo[1,3]dioxol-5-yl-1 H -imidazo[4,5-c]pyridin-2-yl)-furan-3-ylamine	benzo [1,3]dioxol-5-ylamine	MS (ES <sup>+</sup> ) m/e 323 [M+H] <sup>+</sup>
86	4-[1-(2-Methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-1 H -imidazo[4,5-c]pyridin-2-yl]-furan-3-ylamine	2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-ylamine (Heer, J.P.; Harling, John D.; Thompson, Mervyn. <i>Synthetic Communications</i> <b>2002</b> , 32(16), 2555-2563.)	MS (ES <sup>+</sup> ) m/e 348 [M+H] <sup>+</sup>



87	1-[4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenyl]-ethanone oxime	4-amino-acetophenone	MS (ES <sup>+</sup> ) m/e 336 [M+H] <sup>+</sup>
88	4-[1-(2,3,4,5-Tetrahydro-1 H -benzo[c]azepin-8-yl)-1 H -imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	2,3,4,5-tetrahydro-1 H -benzo[c]azepin-8-ylamine (Grunewald, G.L.; Dahanukar, V.H.; Criscione, K.R. <i>Bioorganic &amp; Medicinal Chemistry</i> <b>2001</b> , 1957-1965.)	MS (ES <sup>+</sup> ) m/e 348 [M+H] <sup>+</sup>
89	7-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-3,4-dihydro-2 H -isoquinolin-1-one	7-amino-3,4-dihydro-2 H -isoquinolin-1-one (Lee, N-H.; Lee, C-S.; Jung, D-S. <i>Tetrahedron Lett.</i> <b>1998</b> , 39, 1385-1388.)	MS (ES <sup>+</sup> ) m/e 348 [M+H] <sup>+</sup>
90	4-[2-(4-Amino-furazan-3-yl)-	4-amino-benzonitrile	MS (ES <sup>+</sup> ) m/e 337 [M+H] <sup>+</sup>

	imidazo[4,5- c ]pyridin-1-yl]- N - hydroxy- benzamidine		
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**Example 91: N-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenyl}-N,N',N'-trimethyl-ethane-1,2-diamine**



**5 Step 1: N, N, N'-Trimethyl- N'-(4-nitro-phenyl)-ethane-1,2-diamine**

To a solution containing 1.52 g of 4-nitro-*N*-methylaniline (10 mmol) in 30 mL THF, was added 0.8 g of sodium hydride (60% dispersion in oil, 20 mmol). After 5 minutes at room temperature, 2.59 g of 2-(dimethylamino)ethyl chloride hydrochloride (18 mmol) and 0.4g of sodium hydride (60% dispersion in oil, 10 mmol) were added. The reaction was heated at 60 °C for 5 hours. The solvent was concentrated *in vacuo* to yield a residue which was partitioned between ethyl acetate and 2 M sodium hydroxide solution. The organic phase was washed with water(3x), dried over anhydrous sodium sulphate, filtered, and concentrated *in vacuo* to yield the title compound as a brown oil (1.23 g, 55%). MS (ES<sup>+</sup>) m/e 224 [M+H]<sup>+</sup>

15

**Step 2: N-(2-dimethylaminoethyl)-N-methyl-benzene-1,4-diamine**

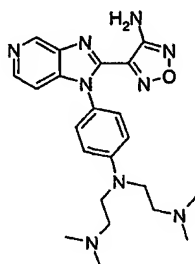
To a solution containing 1.23 g of product from step 1 (5.5 mmol) in 20 mL MeOH, was added 0.6 g of Pd (5 wt. % on activated carbon). The resulting suspension was stirred under

H<sub>2</sub> (50 psi) at room temperature for 3 hours. The reaction mixture was filtered through celite. The filtrate was concentrated *in vacuo* to yield the title compound as a colorless oil (0.71 g, 67%). MS (ES<sup>+</sup>) m/e 194 [M+H]<sup>+</sup>

5 **Step 3: N-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenyl}-N,N',N'-trimethyl-ethane-1,2-diamine**

This example was prepared using the general method of Example 30 using the product from step 2. MS (ES<sup>+</sup>) m/e 379 [M+H]<sup>+</sup>

10 **Example 92: N-{4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenyl}-N-(2-dimethylamino-ethyl)- N', N'-dimethyl-ethane-1,2-diamine**



**Step 1: N-(2-dimethylamino-ethyl)-N',N'-dimethyl-N-(4-nitro-phenyl)-ethane-1,2-diamine**

To a solution containing 2.76 g of 4-nitroaniline (20 mmol) in 20 mL DMF was added 1.60 g of NaH (60% dispersion in oil, 40 mmol). After 2 hours at room temperature, 2-(dimethylamino)ethyl chloride hydrochloride (3.46 g, 24 mmol) was added, and the reaction mixture was heated at 60 °C for 12 hours. The solvent was evaporated *in vacuo* to yield a residue which was partitioned between ethyl acetate and brine. The organic phase was dried over anhydrous sodium sulphate, filtered, and concentrated *in vacuo* to yield a residue.

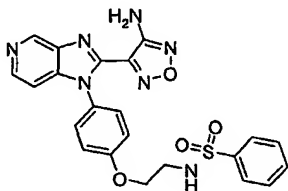
20 Purification of the residue by flash chromatography with 2 % MeOH in CH<sub>2</sub>Cl<sub>2</sub> as the eluent yielded N,N-dimethyl-N'-(4-nitro-phenyl)-ethane-1,2-diamine (2.34 g, 56 %) and the title compound (1.23g, 22%). MS (ES<sup>+</sup>) m/e 281 [M+H]<sup>+</sup>

**Step 2: *N,N*-bis-(2-dimethylamino-ethyl)-benzene-1,4-diamine**

To a solution containing 1.23g of product from step 1 (4 mmol) in 20 mL MeOH, was added 0.8 g of Pd (5 wt. % on activated carbon, 0.4 mmol). The resulting suspension was stirred  
5 under H<sub>2</sub> (50 psi) at room temperature for 3 hours. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to yield the title compound as a colorless oil (1.10 g, 100%). MS (ES<sup>+</sup>) m/e 251 [M+H]<sup>+</sup>

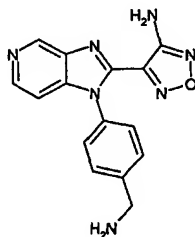
**Step 3: *N*-(4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-*c*]pyridin-1-yl]-phenyl)-*N*-(2-dimethylamino-ethyl)-*N'*, *N'*-dimethyl-ethane-1,2-diamine**

This example was prepared using the general method of Example 30 using the product from step 2. MS (ES<sup>+</sup>) m/e 436 [M+H]<sup>+</sup>

**Example 93: *N*-(2-[4-[2-(4-amino-furazan-3-yl)-imidazo[4,5-*c*]pyridin-1-yl]-phenoxy]-ethyl)-benzenesulfonamide**

The product of example 55 was suspended in dichloromethane (1.25mL) and triethylamine (0.218 mL, 0.487mmol) was added, followed by benzenesulfonyl chloride (0.023mL, 0.182mmol). After 30 minutes, the reaction mixture was partitioned between ethyl acetate  
20 and 2N NaOH. The aqueous phase was washed with ethyl acetate (x1). The combined organic phases were washed with satd. aq. NaCl, dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by preparative HPLC (0-80% CH<sub>3</sub>CN/H<sub>2</sub>O (0.1% TFA), retention time = 7.31 minutes) to yield the title compound as the trifluoroacetate salt (25.7 mg, 44%). MS (ES<sup>+</sup>) m/e 478 [M+H]<sup>+</sup>.

**Example 94: 4-[1-(4-Aminomethyl-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine**



5

**Step 1: {4-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-benzyl}-carbamic acid tert-butyl ester**

The title compound was prepared from (4-aminobenzyl)-carbamic acid tert-butyl ester (*J. Am. Chem. Soc.*, 112, 12, 2000, 2698-2710), using the procedures detailed in Example 30;

10 MS (ES+), m/e 408 [M+H]<sup>+</sup>.

**Step 2: 4-[1-(4-Aminomethyl-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine**

The title compound was prepared from the product of Step 1 using the method of Example 21; MS (ES+), m/e 308 [M+H]<sup>+</sup>.

15 The following examples were prepared using the general two step method of example 94.

	Example	Aniline	Characterisation
95	4-[1-(3-Aminomethyl-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	(3-Amino-benzyl)-carbamic acid tert-butyl ester. ( <i>J. Med. Chem.</i> 42,	MS (ES+) m/e 308 [M+H] <sup>+</sup>

		<u>14</u> , 1999, 2504-2526)	
96	4-[1-(1,2,3,4-Tetrahydro-isoquinolin-5-yl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	5-Amino-3,4-dihydro-1H - isoquinoline-2-carboxylic acid tert-butyl ester. ( <i>Bioorg. Med. Chem.</i> 8, <u>8</u> , 2000, 2085-2094).	MS (ES+) m/e 334 [M+H] <sup>+</sup>
97	4-[1-(1,2,3,4-Tetrahydro-isoquinolin-7-yl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	7-Amino-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (WO 99/14197)	MS (ES+) m/e 334 [M+H] <sup>+</sup>

**Example 98: 4-[1-(2,3-Dihydro-1H-Isoindol-5-yl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine**

**Step 1: 5-nitroisoindoline nitrate**

- 5 Isoindoline (4g, 33.1mmol) was added to 95% sulphuric acid, the reaction was treated carefully with fuming nitric acid (2.2ml) at 0°C and stirred for 1 hour, then the mixture was poured onto ice and the resulting precipitate was collected by filtration and dried *in vacuo* to afford the title compound (4.1g, 46%); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 8.35 (1H, s), 8.35 (1H, d, 8.4Hz), 7.70 (1H, d, 8.4Hz), 4.64 (4H,s).

10

**Step 2: 5-Nitro-1,3-dihydro-isoindole-2-carboxylic acid tert-butyl ester**

The product of Step 1 (3.06g, 13.47mmol) in dichloromethane (50ml) was treated with triethylamine (4.09g, 40.42mmol) followed by di-tertbutyl dicarbonate (3.08g, 14.15mmol) and stirred at room temperature for 3 days. The reaction was then diluted with dichloromethane and washed with 3N citric acid, sodium bicarbonate solution, water and  
5 brine. The organic phase was separated, dried over anhydrous sodium sulfate and evaporated *in vacuo* to afford the title compound (3.5g, 98%); <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.19 (2H, m), 7.26 (1H, m), 4.75 (4H, m), 1.52 (9H,s).

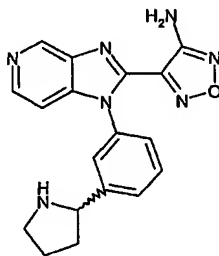
**Step 3: 5-Amino-1,3-dihydro-isoindole-2-carboxylic acid tert-butyl ester**

10 The product of Step 2 (3.5g, 13.25mmol) was dissolved in ethanol (200ml) and treated with 10wt% Palladium on charcoal (1g), and stirred under 1 atm of H<sub>2</sub> for 16 hours. The reaction was filtered and evaporated *in vacuo* to afford the title compound (3.01g, 96%); MS (ES+), m/e 235 [M+H]<sup>+</sup>.

15 **Step4: 4-[1-(2,3-Dihydro-1H-isoindol-5-yl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine**

The amine from Step 3 was reacted according to the general two step method of Example 94 to give the title product. MS (ES+) m/e 320 [M+H]<sup>+</sup>

20 **Example 99: 4-[1-(3-Pyrrolidin-2-yl-phenyl)-1 H -imidazo[4,5- c ]pyridin-2-yl]-furazan-3-ylamine**



**Step 1: 2-(3-Nitro-phenyl)-pyrrole-1-carboxylic acid tert -butyl ester**

A solution of 1-bromo-3-nitrobenzene (1.5g 7.42mmol) in anhydrous 1,2-dimethoxyethane (10ml) was treated sequentially with 1,1-bis(triphenylphosphine) palladium II dichloride (260mg, 0.371mmol), 2M aqueous sodium carbonate (7.4ml), and 1-(t-Butoxycarbonyl)pyrrole-2-boronic acid (1.88g, 8.91mmol) dissolved in ethanol (10ml). The reaction was heated under reflux for 5 hours under argon. The solvent was evaporated and the residue dissolved in dichloromethane, washed with water, brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was purified by silica gel chromatography eluting with a mixture of ether / hexane (5:95) to afford the title compound (1.09g, 51%); MS (ES+) m/e 288 [M+H]<sup>+</sup>.

10

**Step 2: 2-(3-Amino-phenyl)-pyrrolidine-1-carboxylic acid tert-butyl ester**

The product of Step 1 (7.5g, 26.01mmol), was dissolved in ethanol (125ml), and treated with 5wt% Platinum on charcoal (750mg), and stirred under 1 atm of H<sub>2</sub> for 4 days. The reaction was filtered and the filtrate evaporated *in vacuo*. The residue was purified by silica gel chromatography eluting with a mixture of ether / dichloromethane (5:95) to afford the title compound (4.2g, 62%); MS (ES+) m/e 263 [M+H]<sup>+</sup>.

15

**Step 3: 2-{3-[2-(4-Amino-furazan-3-yl)-imidazo[4,5-c]pyridin-1-yl]-phenyl}-pyrrolidine-1-carboxylic acid tert-butyl ester**

The title compound was prepared from the product of Step 2 using the methods of example 30; MS (ES+), m/e 448 [M+H]<sup>+</sup>.

20

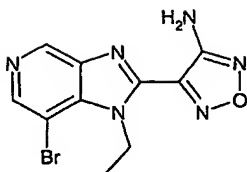
**Step 4: 4-[1-(3-Pyrrolidin-2-yl-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine**

The title compound was prepared from the product of Step 3 using the method of Example 21; MS (ES+), m/e 348 [M+H]<sup>+</sup>.

25

**Example 100: 4-(7-Bromo-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)furazan-3-ylamine**





### Step 1. (3-Bromo-5-nitropyridin-4-yl)ethylamine

To a solution of the product of Example 1 Step 1 (3.0g, 17.9mmol) in acetic acid (40ml) was added bromine (3.12g, 1ml, 19.7mmol) and the mixture was heated at 100°C for 20 hours.

- 5 After cooling the solvent was removed *in vacuo* and the residue was partitioned between dichloromethane and saturated sodium bicarbonate solution. The organic phase was washed with water (x3), dried and evaporated *in vacuo*. Purification of the residue by silica gel chromatography eluting with 50% dichloromethane in ethyl acetate afforded the title compound (1.9g, 43%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 8.73 (1H, s), 8.52 (1H, s), 7.0 (1H, br), 3.25 (2H, m), 1.16 (3H, t, J 7.2Hz).
- 10

### Step 2. 5-Bromo-N<sup>4</sup>-Ethylpyridine-3,4-diamine

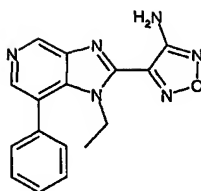
A solution of the product of Step 1 (0.5g, 2mmol) in ethanol (8ml) / water (10ml) was stirred at 60°C and sodium dithionite (2.12g, 12.2mmol) was added portionwise. After 10 minutes

- 15 the mixture was cooled to room temperature, and diluted with water and dichloromethane. The organic phase was dried and evaporated *in vacuo*, the residue was used directly in the next reaction; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 7.76 (1H, s), 7.75 (1H, s), 5.0 (2H, br), 4.46 (1H, t, J 9.6Hz), 3.26 (2H, m), 1.06 (3H, t, J 7.2Hz).

### 20 Step 3. 4-(7-Bromo-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)furan-3-ylamine

The title compound was prepared from the product of Step 2 using the methods of Example 1 Steps 3 and 4; MH (ES+) m/e 309/311 [M+H]<sup>+</sup>.

### Example 101: 4-(1-Ethyl-7-phenyl-1H-imidazo[4,5-c]pyridin-2-yl)furan-3-ylamine



A mixture of the product of Example 100 (50mg, 0.161mmol), phenylboronic acid (30mg, 0.243mmol), bis(triphenylphosphine)palladium (II) dichloride (11mg, 0.0161mmol), sodium carbonate solution (2M, 0.25ml) and toluene (3ml) was heated at 100°C for 3 hours.

- 5 After cooling to room temperature the solvent was evaporated *in vacuo* and the residue purified by silica gel chromatography eluting with 50% dichloromethane in ethyl acetate to afford the title compound; (45mg, 92%). MS (ES+) m/e 307 [M+H]<sup>+</sup>.

The following examples were prepared by the general method described in Example 101.

	Example	Boronic acid	Characterisation
102	4-[1-Ethyl-7-(4-methoxyphenyl)-1H-imidazo[4,5-c]pyridin-2-yl]furazan-3-ylamine	4-Methoxyphenylboronic acid	MS(ES+) m/e 337 [M+H] <sup>+</sup>
103	4-(1-Ethyl-7-thiophen-2-yl-1H-imidazo[4,5-c]pyridin-2-yl)furazan-3-ylamine	Thiophene-2-boronic acid	MS (ES+) m/e 313 [M+H] <sup>+</sup> .

10

The following example was prepared by the general method described in Example 101, replacing the toluene solvent by 1,2-dimethoxyethane.

104	4-[7-(4-Aminomethylphenyl)-1-ethyl-1H-imidazo[4,5-	4-(Aminomethyl)-phenylboronic acid	MS (AP+) m/e 336 [M+H] <sup>+</sup> .
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	c]pyridin-2-yl]furazan-3-ylamine	hydrochloride	
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The following example was prepared by the general method described in Example 101, replacing the toluene solvent by dioxane.

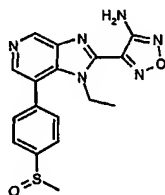
	Example	Boronic Acid	Characterization
<b>105</b>	4-[7-(3-Ethoxy-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	3-Ethoxyphenylboronic acid	MS (ES+) m/e 351 [M+H] <sup>+</sup>
<b>106</b>	4-[1-Ethyl-7-(2-fluoro-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	2-Fluorophenylboronic acid	MS (ES+) m/e 325 [M+H] <sup>+</sup>
<b>107</b>	4-[1-Ethyl-7-(4-methanesulfonyl-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	4-(Methanesulfonyl)benzene boronic acid	MS (ES+) m/e 385 [M+H] <sup>+</sup>
<b>108</b>	4-[1-Ethyl-7-(4-trifluoromethyl-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	4-Trifluoromethylbenzeneboronic acid	MS (ES+) m/e 375 [M+H] <sup>+</sup>

109	4-[7-(2,4-Difluoro-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	2,4-Difluorophenylboronic acid	MS (ES+) m/e 343 [M+H] <sup>+</sup>
110	4-[1-Ethyl-7-(2-trifluoromethyl-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	2-Trifluoromethylbenzeneboronic acid	MS (ES+) m/e 375 [M+H] <sup>+</sup>
111	4-[1-Ethyl-7-(4-methylsulfanyl-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	4-(Methylthio)benzeneboronic acid	MS (ES+) m/e 353 [M+H] <sup>+</sup>
112	4-[7-(2,6-Dimethyl-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	2,6-Dimethylphenylboronic acid	MS (ES+) m/e 335 [M+H] <sup>+</sup>
113	5-[2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]-2-fluorobenzaldehyde	4-Fluoro-3-formylbenzeneboronic acid	MS (ES+) m/e 353 [M+H] <sup>+</sup>

114	4-[7-(3-Amino-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-furan-3-ylamine	3-Aminobenzeneboronic acid monohydrate	MS (ES+) m/e 322 [M+H] <sup>+</sup>
115	4-[1-Ethyl-7-(3-trifluoromethoxy-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furan-3-ylamine	3-(Trifluoromethoxy)phenyl boronic acid	MS (ES+) m/e 391 [M+H] <sup>+</sup>
116	1-{3-[2-(4-Amino-furan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]-phenyl}-ethanone	3-Acetylphenylboronic acid	MS (ES+) m/e 349 [M+H] <sup>+</sup>
117	N-{4-[2-(4-Amino-furan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]-phenyl}-methanesulfonamide	[(4-Methylsulfonyl)aminophenyl]boronic acid	MS (ES+) m/e 400 [M+H] <sup>+</sup>
118	4-[(Bis-trifluoromethyl)-phenyl]-ethyl-1H-imidazo[4,5-c]pyridin-2-yl-furan-3-ylamine	3,5-Bis(trifluoromethyl)-benzeneboronic acid	MS (ES+) m/e 443 [M+H] <sup>+</sup>

119	4-[2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]-2-fluorobenzaldehyde	3-Fluoro-4-formylbenzeneboronic acid	MS (ES+) m/e 353 [M+H] <sup>+</sup>
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**Example 120.** 4-[1-Ethyl-7-(4-methanesulfinyl-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine



5 A solution of the product from Example 111 (0.030g, 0.085mmol) in dichloromethane (4 mL), was cooled to  $-78^{\circ}\text{C}$  under Argon, and was treated with mCPBA (0.029g, 0.17mmol). Allowed the reaction mixture to warm to room temperature and stir for 6 hours. The reaction was reduced *in-vacuo*, then was dissolved in DMSO (1 mL), and purified on the Gilson via reverse-phase HPLC to afford the title compound (12mg, 38%); MS (ES+) m/e

10 369 [M+H]<sup>+</sup>.

The following example was prepared by the general method described in Example 101, replacing the toluene solvent by DMF.

	Example	Boronic Acid	Characterization
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121	5-[2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]-thiophen-2-yl)-carbaldehyde	5-Formyl-2-thiopheneboronic acid	MS (ES+) m/e 355 [M+H] <sup>+</sup>
122	4-(7-Benzo[b]thiophen-3-yl-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine	Benzothiophene-3-boronic acid	MS (ES+) m/e 363 [M+H] <sup>+</sup>
123	4-[1-Ethyl-7-(4-methylthiophen-2-yl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	4-Methylthiophene-2-boronic acid	MS (ES+) m/e 327 [M+H] <sup>+</sup>
124	4-[1-Ethyl-7-(5-phenylthiophen-2-yl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	5-Phenylthiophene-2-boronic acid	MS (ES+) m/e 389 [M+H] <sup>+</sup>

The following examples were prepared by the general method described in Example 101, replacing the toluene solvent by 1,2-dimethoxyethane, and palladium bis(triphenylphosphine)palladium (II) dichloride catalyst with

5 tetrakis(triphenylphosphine)palladium (0).

125	4-(7-Benzo[1,3]dioxol-5-yl-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)furazan-3-ylamine	3,4-Methylenedioxyphenyl boronic acid	MS (ES+) m/e 351 [M+H] <sup>+</sup>
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126	4-(1-Ethyl-7-pyridin-4-yl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl)furazan-3-ylamine	4-Pyridylboronic acid	MS (ES+) <i>m/e</i> 308 [M+H] <sup>+</sup> .
127	4-(1-Ethyl-7-pyridin-3-yl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl)furazan-3-ylamine	3-Pyridylboronic acid	MS (ES+) <i>m/e</i> 308 [M+H] <sup>+</sup> .
128	4-(1-Ethyl-7-furan-3-yl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl)furazan-3-ylamine	3-Furylboronic acid	MS (ES+) <i>m/e</i> 297 [M+H] <sup>+</sup> .
129	4-(1-Ethyl-7-thiophen-3-yl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl)furazan-3-ylamine	3-Thiopheneboronic acid	MS (ES+) <i>m/e</i> 313 [M+H] <sup>+</sup> .
130	4-[1-Ethyl-7-(4-phenoxy-phenyl)-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl]furazan-3-ylamine	4-Phenoxybenzene boronic acid	MS (ES+) <i>m/e</i> 399 [M+H] <sup>+</sup> .
131	4-(1-Ethyl-7-quinoline-8-yl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl]furazan-3-ylamine	8-Quinoline boronic acid	MS (ES+) <i>m/e</i> 358 [M+H] <sup>+</sup> .
132	4-[7-(3,5-Dimethyl-isoxazole-4-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl]furazan-3-ylamine	4-(3,5-Dimethylisoxazole) boronic acid	MS (ES+) <i>m/e</i> 326 [M+H] <sup>+</sup> .
133	4-[1-Ethyl-7-(4-fluoro-phenyl)-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl]furazan-3-ylamine	4-Fluorobenzene boronic acid	MS (ES+) <i>m/e</i> 346 [M+H] <sup>+</sup> .



134	4-[1-Ethyl-7-(4-indol-5-yl)-1- <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2- yl]furazan-3-ylamine	5-Indolylboronic acid acid	MS (ES+) <i>m/e</i> 325 [M+H] <sup>+</sup> .
135	3-[2-(4-Amino-furazan-3-yl)-1- ethyl-1- <i>H</i> - imidazo[4,5, <i>c</i> ]pyridin-7-yl]- benzonitrile	3-Cyanophenyl boronic acid	MS (ES+) <i>m/e</i> 332 [M+H] <sup>+</sup> .
136	4-[2-(4-Amino-furazan-3-yl)-1- ethyl-1- <i>H</i> - imidazo[4,5, <i>c</i> ]pyridin-7-yl]- phenol	4-Hydroxyphenyl boronic acid	MS (ES+) <i>m/e</i> 323 [M+H] <sup>+</sup> .
137	N-{3-[2-(4-Amino-furazan-3- yl)-1-ethyl-1- <i>H</i> - imidazo[4,5, <i>c</i> ]pyridin-7-yl]- phenyl}-acetamide	3-Acetamidophenyl boronic acid	MS (ES+) <i>m/e</i> 364 [M+H] <sup>+</sup> .
138	4-[2-(4-Amino-furazan-3-yl)-1- ethyl-1- <i>H</i> - imidazo[4,5, <i>c</i> ]pyridin-7-yl]- benzonitrile	4-Cyanophenyl boronic acid	MS (ES+) <i>m/e</i> 332 [M+H] <sup>+</sup> .
139	4-[1-Ethyl-7-(3- trifluoromethyl-phenyl)-1 <i>H</i> - imidazo[4,5- <i>c</i> ]pyridin-2- yl]furazan-3-ylamine	3-Trifluoromethylphenyl boronic acid	MS (ES+) <i>m/e</i> 375 [M+H] <sup>+</sup> .
140	{3-[2-(4-Amino-furazan-3-yl)- 1-ethyl-1- <i>H</i> - imidazo[4,5, <i>c</i> ]pyridin-7-yl]-	(3-Hydroxymethyl) phenyl boronic acid	MS (ES+) <i>m/e</i> 337 [M+H] <sup>+</sup> .

	phenyl]-methanol		
141	3-[2-(4-Amino-furazan-3-yl)-1-ethyl-1- H-imidazo[4,5,c]pyridin-7-yl]- N,N-dimethyl-benzamide	N,N-Dimethylbenzamide- 3-boronic acid	MS (ES+) m/e 378 [M+H] <sup>+</sup> .
142	4-{1-Ethyl-7-[4-(5-methyl- [1,2,4]Oxadiazole-3-yl)- phenyl]-1 H-imidazo[4,5- c]pyridin-2-yl]}furazan-3- ylamine	4-(5-Methyl- [1,2,4]Oxadiazol-3- yl)benzene boronic acid [prepared from the corresponding bromide (WO9743262) using the general procedure of Bagley <i>et al Tetrahedron Lett.</i> 2000, 41(35), 6901.]	MS (ES+) m/e 389 [M+H] <sup>+</sup> .
143	4-[2-(4-Amino-furazan-3-yl)-1-ethyl-1- H-imidazo[4,5,c]pyridin-7-yl]- benzamide	4-Aminocarbonylphenyl boronic acid	MS (ES+) m/e 350 [M+H] <sup>+</sup> .
144	3-[2-(4-Amino-furazan-3-yl)-1-ethyl-1- H-imidazo[4,5,c]pyridin-7-yl]- benzamide	3-Aminocarbonylphenyl boronic acid	MS (ES+) m/e 350 [M+H] <sup>+</sup> .
145	4-{7-[4-(2-Amino-ethyl)- phenyl]-1-ethyl-1 H- imidazo[4,5-c]pyridin-2- yl]}furazan-3-ylamine	4-(2-Amino-ethyl)- benzene boronic acid (WO9910022)	MS (ES+) m/e 350 [M+H] <sup>+</sup> .

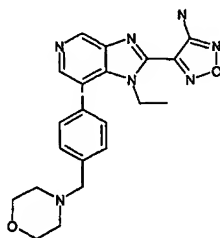
146	4-[7-(3-aminomethyl-phenyl)-1-ethyl-1 H -imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	3-Aminomethyl-phenyl boronic acid	MS (ES+) m/e 336 [M+H] <sup>+</sup>
147	4-(1-ethyl-7-o-tolyl-1 H-imidazo[4,5]pyridin-2-yl-furazan-3-ylamine	2-Methylphenyl boronic acid	MS (ES+) m/e 322 [M+H] <sup>+</sup>

The following example was prepared by the general method described in Example 101, replacing the toluene solvent by *N,N*-dimethylformamide and replacing bis(triphenylphosphine)palladium (II) dichloride with 1,1' -bis

5 (diphenylphosphino)ferrocenedichloropalladium(II) chloroform complex.

148	4-[2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]-benzaldehyde	4-Formyl phenyl boronic acid	MS (ES+) m/e 335 [M+H] <sup>+</sup>
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**Example 149: 4-[1-Ethyl-7-(4-morpholin-4-ylmethyl-phenyl)-1 H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine**



10 To a solution of the product of Example 148 (65mg, 0.19mmol) in methanol (5ml) was added morpholine (33mg, 0.033ml, 0.38mmol), acetic acid (0.2ml) and (polystyrylmethyl) trimethylammonium cyanoborohydride (94mg, 0.38mmol). This mixture was stirred for 18 hours. The (polystyrylmethyl)trimethylammonium cyanoborohydride was filtered off and the

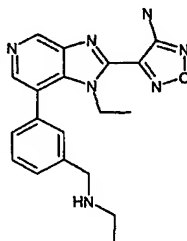
residue concentrated in *vacuo*. The residue was purified by silica gel chromatography eluting with DCM:methanol (40:1) to afford the title compound (21mg, 13%); MS (ES+) *m/e* 406 [M+H]<sup>+</sup>.

The following compounds were prepared by the general method described in

5 Example 149 from the product of Example 148.

	Example	Amine	Characterisation
150	4-[1 Ethyl-7-(4-ethylaminomethyl-phenyl)-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl]furazan-3-ylamine	Ethylamine in THF (1M)	MS (ES+) <i>m/e</i> 364 [M+H] <sup>+</sup>
151	4-{4-[2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-7-yl]-benzylamino}-piperidine-1-carboxylic acid <i>tert</i> -butyl ester	4-Amino-piperidine-1-carboxylic acid <i>tert</i> -butyl ester	MS (ES+) <i>m/e</i> 519 [M+H] <sup>+</sup>
152	4-[1-Ethyl-7-(4-pyrrolidin-1-ylmethyl-phenyl)-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl]-furazan-3-ylamine	Pyrrolidine	MS (ES+) <i>m/e</i> 390 [M+H] <sup>+</sup>

**Example 153: 4-[1 Ethyl-7-(3-ethylaminomethyl-phenyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]furazan-3-ylamine**



10 **Step1: 3-[2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-7-yl]-benzaldehyde**

The crude title compound was prepared from the 3-formylphenyl boronic acid using the method of Example 148.

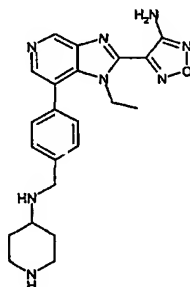
**Step2: 4-[1 Ethyl-7-(3-ethylaminomethyl-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]furazan-3-ylamine**

- 5 The product of Step 1 was converted into the title compound by reaction with ethylamine (1M in THF) according to the general method of Example 149. MS (ES+) m/e 364 [M+H]<sup>+</sup>

The following compounds were prepared by the general method described in Example 149 from the product of Example 153 Step 1.

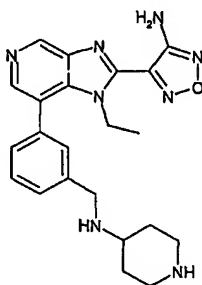
	Example	Amine used	Characterisation
154	4-[7-(3-Dimethylaminomethyl-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	Dimethylamine	MS(ES+) m/e 365 [M+H] <sup>+</sup>
155	4-[1-ethyl-7-(3-morpholin-4-ylmethyl-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	Morpholine	MS (ES+) m/e 406 [M+H] <sup>+</sup>
156	4-[1-Ethyl-7-(3-pyrrolidin-1-ylmethyl-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	Pyrrolidine	MS (ES+) m/e 390 [M+H] <sup>+</sup>

- 10 **Example 157. {4-[2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]-benzyl}-piperidin-4-yl-amine**



The title compound was prepared from the product of Example 151 using the method described in Example 21; MS (ES+) m/e 419 [M+H]<sup>+</sup>

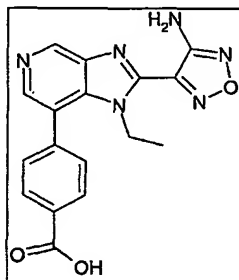
**Example 158.**    **{3-[2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-7-yl]-**  
**5 benzyl]-piperidin-4-yl-amine**



The title compound was prepared from 4-amino-piperidine-1-carboxylic acid *tert*-butyl ester and the product of Example 153 Step 1 using the method of Example 149, followed by the method described in Example 21. MS (ES+) m/e 419 [M+H]<sup>+</sup>

10

**Example 159.**    **4-[2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-7-yl]-**  
**benzoic acid**



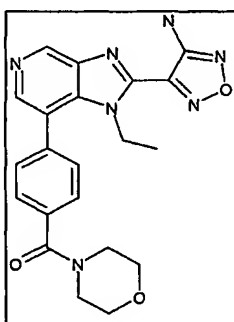
To a solution of the product from Example 100 (1.5 g, 4.85 mmol) in 1,4-Dioxane (50 ml) was added 4-carboxybenzene boronic acid (1.20 g, 7.23 mmol), sodium carbonate (7 ml of a 2 M solution ) and tetrakis(triphenylphosphine)palladium(0) (1.12 g, 0.97 mmol). The reaction mixture was heated to reflux with stirring for 18 hours and allowed to cool. The

reaction mixture was filtered and washed with ether (5 x, 100 ml) to afford the title compound as a yellow solid (0.594 g, 35 %); MS (ES+) m/e 351 [M+H]<sup>+</sup>.

The following example was prepared by the method of Example 159

	Example	Boronic acid	Characterisation
160	3-[2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-7-yl]-benzoic acid	3-carboxybenzene boronic acid	MS (ES+) m/e 351 [M+H] <sup>+</sup> .

5    **Example 161.**        4-[2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-]pyridin-7-yl]-phenyl-1-morpholin-4-yl-methanone



The product from Example 159 in DMF (5 ml) (0.200 g, 571  $\mu$ mol) was treated with  
 10    PyBop (892 mg, 1.71 mmol), DIPEA (297  $\mu$ l, 1.71 mmol) and morpholine (149  $\mu$ l, 1.71 mmol). The mixture was stirred at room temperature for 18 hours and the crude product concentrated to a glassy solid. The crude product was purified on a Gilson HPLC system to yield the titled compound as a solid (0.129 g, 54 %); MS (ES+) m/e 420 [M+H]<sup>+</sup>.

The following compounds were prepared by the general method described in

15    **Example 161** from the product of Example 159.

	Example	Amine	Characterisation
162	4-[2-(4-Amino-furazan-3-yl)-1-	phenethyl amine	MS (ES+) m/e 454

	ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-7-yl]- <i>N</i> -phenethyl-benzamide		[M+H] <sup>+</sup>
163	4-[2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5-]pyridin-7-yl]-phenyl)-1-pyrrolidin-1-yl-methanone	Pyrrolidine	MS (ES+) m/e 404 [M+H] <sup>+</sup>
164	4-[2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-7-yl]- <i>N</i> -benzyl-benzamide	benzylamine	MS (ES+) m/e 440 [M+H] <sup>+</sup>
165	4-[2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-7-yl]-phenyl)-methanoyl)-pyrrolidine-2- carboxylic acid methyl ester	L-proline methyl ester	MS (ES+) m/e 462 [M+H] <sup>+</sup>
166	4-[2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-7-yl]-phenyl)-1-(4-methyl-piperazin-1-yl)-methanone	1-methyl piperazine	MS (ES+) m/e 433 [M+H] <sup>+</sup>

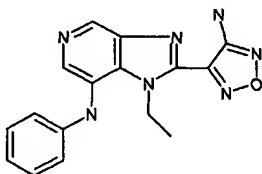
The following compounds were prepared by the general method described in Example 161 from the product of Example 160.

	Example	Amine	Characterisation
167	3-[2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-7-yl]- <i>N</i> -phenethyl-benzamide	phenethyl amine	MS (ES+) m/e 454 [M+H] <sup>+</sup>
168	3-[2-(4-Amino-furazan-3-yl)-1-	benzylamine	MS (ES+) m/e 440



	ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-7-yl]- <i>N</i> -benzyl-benzamide		[M+H] <sup>+</sup>
169	3-[2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-7-yl]-phenyl)-methanoyl)-pyrrolidine-2- carboxylic acid methyl ester	L-proline methyl ester	MS (ES+) m/e 462 [M+H] <sup>+</sup>
170	3-[2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-7-yl]-phenyl)-1-(4-methyl-piperazin-1-yl)-methanone	1-methyl piperazine	MS (ES+) m/e 433 [M+H] <sup>+</sup>
171	3-[2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5-]pyridin-7-yl]-phenyl)-1-morpholin-4-yl-methanone	morpholine	MS (ES+) m/e 420 [M+H] <sup>+</sup>

**Example 172.** [2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-7-yl]-phenyl-amine



5

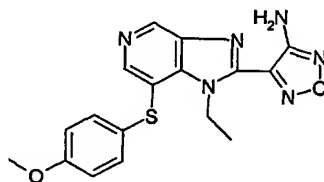
Under Ar, a solution of the product from Example 100 (24 mg, 77.6  $\mu$ mol) in 1,4-dioxane (0.8 ml) and toluene (1.2 ml) was treated with Tris(dibenzylidene-acetone)dipalladium (7.2 mg, 7.8  $\mu$ mol), racemic-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (9.7 mg, 15.6  $\mu$ mol), aniline (8.5  $\mu$ l, 93.1  $\mu$ mol), and sodium *tert*-butoxide (10.5 mg, 108.6  $\mu$ mol).

mol). This mixture was then heated to 175 °C by microwave for 45 min. After cooled to ambient temperature, the reaction mixture was diluted with ethyl acetate (30 ml), filtered through a celite pad and then the filtrate was concentrated *in vacuo*. The residue was purified with reverse phase HPLC (10% MeCN/H<sub>2</sub>O → 80% MeCN/H<sub>2</sub>O), to afford the title compound, (6.3 mg, 24%); MS (ES+) m/e 322 [M+H]<sup>+</sup>.

The following examples were obtained by the method of Example 172.

	Example	Aniline	Characterisation
173	[2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-7-yl]-pyridin-3-yl-amine	3-aminopyridine	MS(ES+) m/e 323 [M+H] <sup>+</sup>
174	[2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-7-yl]-(4-morpholin-4-yl-phenyl)-amine	4-morpholinoaniline	MS (ES+) m/e 407 [M+H] <sup>+</sup>

**Example 175.** 4-[1-Ethyl-7-(4-methoxy-phenylsulfanyl) -1*H*-imidazo[4,5-*c*]pyridin-2-yl]-furazan-3-ylamine



10

Under Ar, a solution of the product from Example 100 (53.2 mg, 172 μmol) in 1,4-dioxane (1 ml) and toluene (1.5 ml) was treated with Tris(dibenzylidene-acetone)dipalladium (15 mg, 17 μmol), racemic-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (20 mg, 34 μmol), 4-

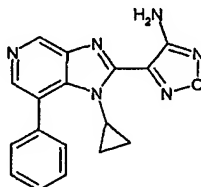
methoxybenzenethiol (261, 206 mol), and sodium *tert*-butoxide (23.5 mg, 241 mol).

This mixture was then heated to 175 °C by microwave for 1 h. After cooled to ambient temperature, the reaction mixture was diluted with ethyl acetate (30 ml) and methanol (30 ml), filtered through a celite pad and then the filtrate was concentrated *in vacuo*. The residue was purified with flash chromatography (hexanes/ethyl acetate 2:1), to afford the title compound, (35.6 mg, 56%); MS (ES+) *m/e* 369 [M+H]<sup>+</sup>.

The following example was obtained by the method of Example 175.

	Example	thiophenol	Characterization
176	4-[1-Ethyl-7-phenyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl]-furazan-3-ylamine	benzenethiol	MS(ES+) <i>m/e</i> 339 [M+H] <sup>+</sup>

Example 177: 4-(1-cyclopropyl-7-phenyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine



#### Step 1. 3-Bromo-5-nitropyridin-4-ol

To a suspension of 4-hydroxy-3-nitropyridine (7.00g, 50 mmol) in water (50 ml) was added bromine (3.23ml, 63 mmol) dropwise at room temperature. The resulting mixture was stirred for one hour then heated to 50°C for two hours. After cooling to room temperature and stirring for a further hour the product was filtered off, washed with water and dried under vacuum for two days, affording 9.54g (87%); MS (AP-) *m/e* 217/219 [M+H]<sup>+</sup>.

#### Step 2. 3-Bromo-4-chloro-5-nitro-pyridine

To phosphorous oxychloride (50 ml) cooled in ice was slowly added the product of step 1 (6.57g, 30 mmol). To the resulting stirred solution was added N,N-diethylaniline (4.77ml, 30 mmol) dropwise. The resulting mixture was warmed to room temperature, then heated to reflux for two hours. After this time the mixture was concentrated under vacuum and the  
5 residue poured onto ice. The mixture was extracted into diethyl ether and the organic phase washed twice with water, followed by once with brine before concentrating to a brown oil which solidified on standing, 8.01g (>100%); <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.94 (1H, s), 8.93 (1H, s).

**Step 3. (3-Bromo-5-nitro-pyridin-4-yl)-cyclopropyl-amine**

10 To a solution of the product of Step 2 (8.01g, ca. 30mmol) in dichloromethane (100ml) at 0°C was added cyclopropylamine (4.16ml, 60 mmol) drop-wise. The resulting mixture was stirred overnight at room temperature, then concentrated under vacuum to a residue and re-dissolved in ethyl acetate, basifying with sodium bicarbonate. The organic phase was washed with water three times, followed by twice with brine before concentrating under  
15 vacuum to a crude solid. This oil was purified by column chromatography eluting with a gradient of 50% DCM/hexane to DCM affording product as a yellow solid, 6.22g (80%); MS (ES+) m/e 258/260 [M+H]<sup>+</sup>.

**Step 4. 5-Bromo-N<sup>4</sup>-cyclopropyl-pyridine-3,4-diamine**

20 To a stirred solution of the product obtained from Step 3 (2.95g, 11.4mmol) in glacial acetic acid (50ml) was added iron dust (3.35g, 60mmol). The resulting mixture was stirred at 80°C for 90 minutes, after which it was filtered through Celite and the liquor concentrated under vacuum. The crude product was re-dissolved in ethyl acetate, basified with sodium bicarbonate and refiltered. Th organic phase was washed with water three times, followed by  
25 twice with brine before concentrating under vacuum to give the product. Passed through a silica plug affording product as an oil, 1.65g (63%); MS (ES+) m/e 228/230 [M+H]<sup>+</sup>.

**Step 5. 4-(7-Bromo-1-cyclopropyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine**

The title compound was prepared from the product of Step 4 using the method of Example 1 Steps 3 and 4; MS (ES+) m/e 321/323 [M+H]<sup>+</sup>.

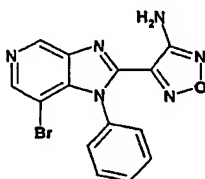
**5 Step 6. 4-(1-Cyclopropyl-7-phenyl-1H-imidazo[4,5-c]pyridin-2-yl)furazan-3-ylamine**

The title compound was prepared from the product of Step 5 and phenylboronic acid using the method of Example 101; MS (ES+) m/e 319 [M+H]<sup>+</sup>.

The following compounds were prepared from the product of Example 177, Step 5 and the corresponding boronic acid using the general method of Example 101

<b>178</b>	4-[7-(4-Aminomethylphenyl)-1-cyclopropyl-1H-imidazo[4,5-c]pyridin-2-yl]furazan-3-ylamine	4-(Aminomethyl)-phenylboronic acid hydrochloride	MS (ES+) m/e 348 [M+H] <sup>+</sup> .
<b>179</b>	4-(1-Cyclopropyl-7-thiophen-2-yl-1H-imidazo[4,5-c]pyridin-2-yl)furazan-3-ylamine	2-Thiopheneboronic acid	MS (ES+) m/e 325 [M+H] <sup>+</sup> .

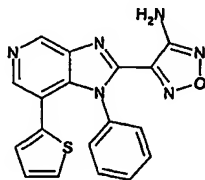
10

**Example 180. 4-(7-Bromo-1-phenyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine**

The title compound was prepared from the product of Example 177 Step 2 and aniline using the method described in Example 177 Steps 3-5; MS (ES+) m/e 358 [M+H]<sup>+</sup>.

15

**Example 181. 4-(1-Phenyl-7-thiophen-2-yl-1H-imidazo[4,5-c] pyridin-2-yl)-furazan-3-ylamine**



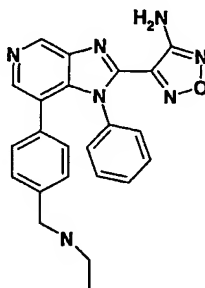
A stirred mixture of the product from Example 180 (50 mg, 0.14 mmol), thiophene-2-boronic acid (27 mg, 0.21 mmol) and Pd(dppf)<sub>2</sub>Cl<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub> (11 mg, 0.014 mmol) in 3.5 ml of 2.5:1 Dioxane/2 M K<sub>2</sub>CO<sub>3</sub> contained in a 20 ml pressure tube was heated to 110 °C for 18 h. The resulting biphasic mixture was cooled to room temperature. The organic layer (top) was removed with pipet, filtered to remove the Pd. The aqueous layer was extracted once with EtOAc. EtOAc was combined with the organic filtrate, washed with sat'd NaHCO<sub>3</sub>, water, brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and reduced in vacuo. the residue was purified by silica gel chromatography eluting with 10% MeOH in CHCl<sub>3</sub>, to afford the title compound, (9 mg, 18%); MS (ES<sup>+</sup>) m/e 361 [M+H]<sup>+</sup>.

The following examples were prepared from the product of Example 180 using the method described in Example 181.

	Example	Boronic acid	Characterisation
182	4-(1,7-Diphenyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine	phenylboronic acid	MS(ES <sup>+</sup> ) m/e 355 [M+H] <sup>+</sup>
183	4-[2-(4-Amino-furazan-3-yl)-1-phenyl-1H-imidazo[4,5-c]pyridin-7-yl]-phenol	4-hydroxybenzene boronic acid	MS (ES <sup>+</sup> ) m/e 371 [M+H] <sup>+</sup>
184	4-[7-(3,5-Dimethyl	3,5-dimethyl	MS (ES <sup>+</sup> ) m/e 374 [M+H] <sup>+</sup>

	isoxazole-4-yl)-1-phenyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl]-furazan-3-ylamine	isoxazole-4-boronic acid	
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**Example 185. 4-[7-(4-Ethylaminomethyl-phenyl)-1-phenyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-furazan-3-ylamine**



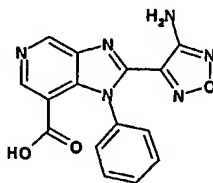
**Step 1. 4-[2-(4-Amino-furazan-3-yl)-1-phenyl-1*H*-imidazo[4,5-*c*]pyridin-7-yl]-benzaldehyde**

A stirred mixture the product of Example 180 (0.2 g, 0.56 mmol), 4-formylbenzeneboronic acid (0.126 g, 0.84 mmol) and Pd(dppf)<sub>2</sub>Cl<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub> (0.046 g, 0.056 mmol) in 6.0 ml of 2.5:1 Dioxane/2 M K<sub>2</sub>CO<sub>3</sub> contained in a 20 ml pressure tube was heated to 110 °C for 18 h. The resulting biphasic mixture was cooled to room temperature. The organic layer (top) was removed with pipet, filtered to remove the Pd. The aqueous layer was extracted once with EtOAc. EtOAc was combined with the organic filtrate, washed with sat'd NaHCO<sub>3</sub>, water, brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and reduced in vacuo. the residue was purified by silica gel chromatography eluting with 10% MeOH in CHCl<sub>3</sub>, to afford the title compound, (0.10 g, 47%); MS (ES<sup>+</sup>) *m/e* 383 [M+H]<sup>+</sup>.

**Step 2. 4-[7-(4-Ethylaminomethyl-phenyl)-1-phenyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-furazan-3-ylamine**

To a stirring solution of the product from step 1 (0.1 g, 0.26mmol) and ethylamine (in THF, 0.12 ml, 0.24 mmol) in methylene chloride (4 ml) was added sodium triacetoxyborohydride (0.055 g, 0.26 mmol) and acetic acid (0.4 ml). The reaction mixture was stirred overnight. The solvent was removed and the residue was washed with sat'd NaHCO<sub>3</sub>, extracted 3 x  
5 with EtOAcwater, dried (Na<sub>2</sub>SO<sub>4</sub>) and reduced in vacuo. The residue was purified by silica gel chromatography eluting with 30% ethyl acetate in hexane, to afford the title compound, (0.016g, 15%); MS (ES+) m/e 411 [M+H]<sup>+</sup>.

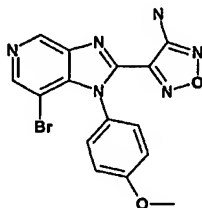
**Example 186. 2-(4-Amino-furazan-3-yl)-1-phenyl-1H-imidazo[4,5-c]pyridine-7-**  
10 **carboxylic acid**



A solution of the product from Example 180 (0.1 g, 0.28 mmol) in tetrahydrofuran (10 ml) at -78°C was treated with 2 M solution lithium diisopropylamide (LDA, 0.28 ml, 0.56 mmol) in hexane under argon. After 5 minutes the solution was treated with a 1.6 M solution of n-butyl lithium (0.52 ml, 0.84 mmol) in hexane at -78°C. The mixture was stirred for 10 mins,  
15 then carbon dioxide gas was bubbled through the solution for 10 mins. The resulting pale yellow suspension was allowed to warm to room temperature over 2 h, water (1 ml) in tetrahydrofuran (3 ml) was cautiously added dropwise and the mixture concentrated in vacuo. The residual solid was washed with ether (2x10 ml) then dissolved in methanol (10  
20 ml) containing glacial acetic acid. The solvent was evaporated and the residue triturated under ether (2 ml) and filtered to give the title compound (10 mg, 11%); MS (ES+) m/e 323 [M+H]<sup>+</sup>.

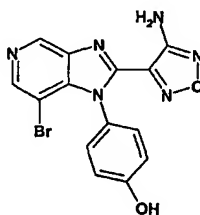


**Example 187.** 4-[7-Bromo-1-(4-methoxy-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine



- 5 The title compound was prepared from the product of Example 177 Step 2 and 4-methoxy-aniline using the method described in Example 177 Steps 3-5; MS (ES+) m/e 388 [M+H]<sup>+</sup>.

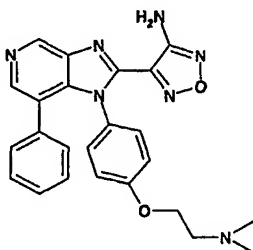
**Example 188.** 4-[2-(4-Amino-furazan-3-yl)-7-bromo-imidazo[4,5-c]pyridin-1-yl]-phenol



10

- To a solution of the product from Example 187 (0.1 g, 0.26 mmol) in anhydrous dichloromethane (10 ml) stirred at 0 °C, was added dropwise boron tribromide (1.0 M solution in dichloromethane, 2.3 ml, 2.3 mmol) and the mixture stirred at room temperature for 16 hours. The reaction was quenched with water (20 ml), basified to pH 14 with 50% sodium hydroxide solution. The aqueous phase was washed with dichloromethane 3x, neutralised with 6 N hydrochloric acid, and the resulting precipitate collected, washed with water 3x, diethyl ether and dried in vacuo to yield the title product (40 mg, 40%); MS (ES+) m/e 374 [M+H]<sup>+</sup>.
- 15

**Example 189.** 4-{1-[4-(2-Dimethylamino-ethoxy)-phenyl]-7-phenyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl}-furazan-3-ylamine



**Step 1.** 4-{7-Bromo-1-[4-(2-dimethylamino-ethoxy)-phenyl]-1*H*-imidazo[4,5-*c*]pyridin-2-yl}-furazan-3-ylamine

The title compound was obtained from the product of Example 188 by the method of Example 41; MS (ES+) *m/e* 444/446 [M+H]<sup>+</sup>.

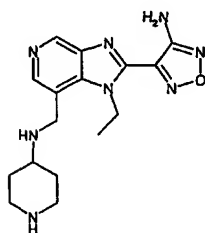
**Step 2.** 4-{1-[4-(2-Dimethylamino-ethoxy)-phenyl]-7-phenyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl}-furazan-3-ylamine

A stirred mixture of the product of Step 1 (0.1 g, 0.23 mmol), phenylboronic acid (41 mg, 0.34 mmol) and Pd(dppf)<sub>2</sub>Cl<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub> (19 mg, 0.023 mmol) in 2.5 ml of 2.5:1 Dioxane/2 M K<sub>2</sub>CO<sub>3</sub> contained in a 20 ml pressure tube was heated to 110 °C for 18 h. The resulting biphasic mixture was cooled to room temperature. The organic layer (top) was removed with pipet, filtered to remove the Pd. The aqueous layer was extracted once with EtOAc. EtOAc was combined with the organic filtrate, washed with sat'd NaHCO<sub>3</sub>, water, brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and reduced in vacuo. The residue was purified by silica gel chromatography eluting with 10% MeOH in CHCl<sub>3</sub>, to afford the title compound, (16 mg, 16%); MS (ES+) *m/e* 442 [M+H]<sup>+</sup>.

The following examples were prepared from the product of Example 189, Step 1 using the method of Example 189, Step 2.

	Example	Boronic acid	Characterisation
190	4-[1-[4-(2-Dimethylamino-ethoxy)-phenyl]-7-(4-fluoro-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	4-fluorophenyl boronic acid	MS(ES+) m/e 460 [M+H] <sup>+</sup>

**Example 191: [2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-ylmethyl]-piperidin-4-yl-amine**



5

**Step 1. 2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carbaldehyde**

A solution of the product from Example 100 (0.1g, 0.324mmol) in tetrahydrofuran (4ml) at – 78°C was treated with a 1.6M solution of n-butyllithium (0.6ml, 0.97mmol) in hexanes. After 5 minutes the mixture was treated with dimethylformamide (0.3ml) and allowed to reach

10 room temperature. After 30 minutes at room temperature the reaction was carefully quenched with water and extracted into dichloromethane (x2). The organic layer was then washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and reduced in vacuo. The residue was purified by silica gel chromatography eluting with ethyl acetate, to afford the title compound, (0.034g, 41%); MS (ES+) m/e 259 [M+H]<sup>+</sup>.

15

**Step 2. 4-[[2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-ylmethyl]-amino]-piperidine-1-carboxylic acid *tert*-butyl ester**

The title compound was prepared from the product of Step 1 and 4-Amino-piperidine-1-carboxylic acid *tert*-butyl ester according to the general method of Example 149; MS (ES+) *m/e* 443 [M+H]<sup>+</sup>.

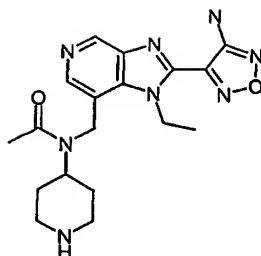
**5 Step 3. [2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-7-ylmethyl]-piperidin-4-yl-amine**

A solution of the product from Step 2 (0.075g, 0.17mmol) in dichloromethane (1ml) was treated with trifluoroacetic acid (1ml). After 2 hours the reaction was reduced *in vacuo*, dissolved in methanol and applied to a SCX ion exchange column and eluted with methanol  
 10 and then a mixture of methanol/0.880 ammonia (9:1). The basic fractions were then reduced to afford the title compound, (0.053g, 91%); MS (ES+) *m/e* 343 [M+H]<sup>+</sup>.

The following examples were prepared from the product of Example 191 Step 1 using the method described in Example 149 followed by the method of Example 191 Step 3

	Example	Amine	Characterisation
192	1-[2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-7-ylmethyl]-piperidin-4-ylamine	Piperidin-4-yl-carbamic acid <i>tert</i> -butyl ester	MS(ES+) <i>m/e</i> 343 [M+H] <sup>+</sup>
193	4-(1-Ethyl-7-piperazin-1-ylmethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl)-furazan-3-ylamine	piperazine-1-carboxylic acid <i>tert</i> -butyl ester	MS (ES+) <i>m/e</i> 329 [M+H] <sup>+</sup>

**15 Example 194. *N* -[2-(4-Amino-furazan-3-yl)-1-ethyl-1 *H* -imidazo[4,5-*c*]pyridin-7-ylmethyl]-*N*-piperidin-4-yl-acetamide**



**Step 1. 4-{Acetyl-[2-(4-amino-furazan-3-yl)-1-ethyl-1H-imidazo [4,5-c]pyridin-7-ylmethyl]-amino}-piperidine-1-carboxylic acid *tert*-butyl ester**

- 5 The title compound from Example 191, Step 2 (145mg, 0.3mmol) in dichloromethane at 0 °C was treated with potassium carbonate (90mg, 0.66mmol) followed by acetyl chloride (26mg, 0.33mL), and the mixture was stirred at room temperature for 1 hour. Purification of the residue by silica gel chromatography eluting with 10% methanol / dichloromethane afforded the title compound (68mg, 10%). MS (ES+) m/e 484 [M+H]<sup>+</sup>.

10

**Step 2. N-[2-(4-Amino-furazan-3-yl)-1-ethyl-1 H -imidazo[4,5-c]pyridin-7-ylmethyl]-N-piperidin-4-yl-acetamide.**

The title compound was prepared from the product of Step 1 and 4-Amino-piperidine-1-carboxylic acid *tert*-butyl ester according to the general method of Example 191 Step 3. MS

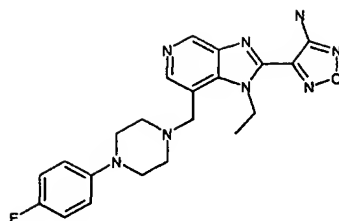
- 15 (ES+) m/e 384 [M+H]<sup>+</sup>.

The following examples were prepared from the product of Example 191 Step 1 using the method described in Example 149.

	Example	Amine	Characterisation
195	4-{7-[(4-Bromo-benzylamino)-methyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-	4-Bromo-benzylamine	MS(ES+) m/e 429 [M+H] <sup>+</sup>

	ylamine		
196	4-{1-Ethyl-7-[(3-methoxy-benzylamino)-methyl]-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl}-furazan-3-ylamine	3-Methoxy-benzylamine	MS (ES+) m/e 380 [M+H] <sup>+</sup>
197	4-(1-Ethyl-7-morpholin-4-ylmethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl)furazan-3-ylamine	Morpholine	MS(ES+) m/e 330 [M+H] <sup>+</sup>
198	4-(1-Ethyl-7-piperidin-1-ylmethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl)furazan-3-ylamine	Piperidine	<sup>1</sup> H NMR (D <sup>6</sup> DMSO) δ 9.06 (1H, s), 8.27 (1H, s), 6.96 (2H, br s), 5.00 (2H, q, J 8, 13Hz), 3.77 (2H, s), 2.50-2.25 (4H, m), 1.56-1.30 (9H, m)
199	4-{1-Ethyl-7-(4-ethylpiperazin-1-ylmethyl)-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl}furazan-3-ylamine	1-Ethylpiperazine	MS(ES+) m/e 357 [M+H] <sup>+</sup>

**Example 200:** 4-{1-Ethyl-7-[4-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-1*H*-imidazo[4,5-*c*]pyridin-2-yl}furazan-3-ylamine



The product of Example 191 Step 1 (0.10g, 0.38mmole) in 1,2-dichloroethane (5ml) was treated with 1-(4-fluorophenyl)piperazine (0.10g, 0.58mmole) and stirred at ambient temperature for 15 minutes. Sodium triacetoxymethylborohydride (0.16g, 0.76mmole) was added and the reaction mixture stirred at ambient temperature for 18 hours. The mixture was diluted with dichloromethane, washed (x2) with saturated sodium hydrogen carbonate solution followed by saturated brine, dried over magnesium sulphate and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with ethyl acetate to afford the title compound; MS(ES+) m/e 357 [M+H]<sup>+</sup>.

The following examples were prepared from the product of Example 191 Step 1 using the method described in Example 200.

	Example	Amine	Characterisation
201	4-{1-Ethyl-7-[(3-pyrrolidin-1-yl-propylamino)-methyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine	1-(3-aminopropyl)pyrrolidine	MS(ES+) m/e 371 [M+H] <sup>+</sup>
202	[2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-ylmethyl]-methyl-(1-methyl-piperidin-4-yl)-	1-Methyl-4-(methylamino)-piperidine	MS(ES+) m/e 371 [M+H] <sup>+</sup>

	amine		
203	4-[1-Ethyl-7-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-ylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	(S)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine	MS(ES+) m/e 397 [M+H] <sup>+</sup>
204	2-{4-[2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-ylmethyl]-piperazin-1-yl}-1-pyrrolidin-1-yl-ethanone	1-(Pyrrolidinocarbonylmethyl)piperazine	MS(ES+) m/e 440 [M+H] <sup>+</sup>
205	4-[1-Ethyl-7-[(2-pyrrolidin-1-yl-ethylamino)-methyl]-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	1-(2-Aminoethyl)pyrrolidine	MS(ES+) m/e 357 [M+H] <sup>+</sup>
206	4-[1-Ethyl-7-(4-methylpiperazin-1-ylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	N-Methylpiperazine	MS(ES+) m/e 343 [M+H] <sup>+</sup>
207	4-[1-Ethyl-7-((R)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-ylmethyl)-	(S)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine (de Costa	MS(ES+) m/e 397 [M+H] <sup>+</sup>



	1 <i>H</i> -imidazo[4,5- <i>c</i> ] pyridin-2-yl]- furazan-3- ylamine	<i>et al</i> , J. Med.Chem., 1992; 35; 23, 4334-4343)	
208	4-[7-(( <i>S</i> )-3- Dimethylamino- pyrrolidin-1-ylmethyl)-1- ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl]-furazan-3- ylamine	Dimethyl-( <i>S</i> )- pyrrolidin-3-yl- amine (Cesare, P. <i>et al</i> , J. Med.Chem., 1992; 35; 22, 4205-4213)	MS(ES+) <i>m/e</i> 357 [M+H] <sup>+</sup>
209	[2-(4-Amino-furazan-3- yl)-1-ethyl-1 <i>H</i> - imidazo[4,5- <i>c</i> ]pyridin-7- ylmethyl)-(1-methyl- piperidin-4-yl)-amine	1-Methyl-piperidin- 4-ylamine (Brookes <i>et al</i> , J. Chem. Soc., 1957; 3165- 3171)	MS(ES+) <i>m/e</i> 357 [M+H] <sup>+</sup>
210	4-[1-Ethyl-7-(( <i>S</i> )-2- morpholin-4-ylmethyl- pyrrolidin-1-ylmethyl)- 1 <i>H</i> -imidazo[4,5- <i>c</i> ] pyridin-2-yl]-furazan-3- ylamine	4-( <i>S</i> )-1-Pyrrolidin-2- ylmethyl- morpholine (Asami, M. <i>et al</i> , Bull. Chem. Soc. Jpn, 1990; 63, 3, 721- 727)	MS(ES+) <i>m/e</i> 413 [M+H] <sup>+</sup>
211	4-{1-Ethyl-7-[(3- piperidin-1-yl- propylamino)-methyl]- 1 <i>H</i> -imidazo[4,5- <i>c</i> ] pyridin-2-yl]-furazan-3-	3-Piperidin-1-yl- propylamine (Lehman, Chem. Ber., 1894; 27, 2176)	MS(ES+) <i>m/e</i> 385 [M+H] <sup>+</sup>

	ylamine		
212	4-{1-Ethyl-7-[(3-morpholin-4-yl-propylamino)-methyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine	3-Morpholin-4-yl-propylamine (Utermohlen <i>et al</i> , J. Amer.Chem. Soc., 1941; 63, 156-158)	MS(ES+) m/e 387 [M+H] <sup>+</sup>
213	4-(1-Ethyl-7-[(3-(4-methyl-piperazin-1-yl)-propylamino)-methyl]-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine	3-(4-Methyl-piperazin-1-yl)-propylamine (Short, J. H., <i>et al</i> , J. Med.Chem., 1963; 6, 275-283)	MS(ES+) m/e 400 [M+H] <sup>+</sup>
214	4-[1-Ethyl-7-((S)-2-piperidin-1-ylmethyl-pyrrolidin-1-ylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	1-(S)-1-Pyrrolidin-2-ylmethyl-piperidine (Asami, M., <i>Bull. Chem. Soc. Jpn.</i> , 1990, 63(3), 721-7)	MS(ES+) m/e 411 [M+H] <sup>+</sup>
215	4-[7-((3R,5S)-3,5-Dimethylpiperazin-1-ylmethyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)furazan-3-ylamine	cis-2,6-Dimethylpiperazine	MS(ES+) m/e 357 [M+H] <sup>+</sup>
216	4-[1-Ethyl-7-(4-pyrrolidin-1-yl)piperidin-	4-(1-Pyrrolidinyl)piperidi	MS(ES+) m/e 397 [M+H] <sup>+</sup>

	1-ylmethyl)-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl)furazan-3-ylamine	ne	
217	1-{4-[2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-7-ylmethyl]-piperazin-1-yl}-ethanone	1-acetyl piperazine	MS(ES+) m/e 371 [M+H] <sup>+</sup>
218	4-[7-(( <i>R</i> )-3-Dimethylamino-pyrrolidin-1-ylmethyl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl]-furazan-3-ylamine	Dimethyl-( <i>R</i> )-pyrrolidin-3-yl-amine	MS(ES+) m/e 357 [M+H] <sup>+</sup>
219	[2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-7-ylmethyl]-(1-isopropyl-piperidin-4-yl)-amine	1-Isopropyl-4-amino-piperidine	MS(ES+) m/e 385 [M+H] <sup>+</sup>
220	{{( <i>S</i> )-1-[2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-7-ylmethyl]-pyrrolidin-2-yl}-methanol	( <i>S</i> )-1-Pyrrolidin-2-yl-methanol	MS(ES+) m/e 344 [M+H] <sup>+</sup>
221	3-{[2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -	3-Amino-propan-1-ol	MS(ES+) m/e 318 [M+H] <sup>+</sup>

	imidazo[4,5-c]pyridin-7-ylmethyl]-amino)-propan-1-ol		
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The following examples were prepared from the product of Example 191 Step 1 using the method described in Example 200 followed by the method described in Example 191 Step 3.

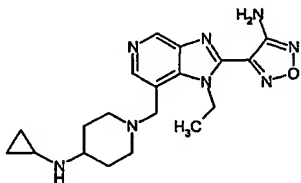
	Example	Amine	Characterisation
222	4-[1-Ethyl-7-(pyrrolidin-3-ylaminomethyl)-1 <i>H</i> -imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	3-Amino-pyrrolidine-1-carboxylic acid <i>tert</i> -butyl ester (Falgueyret, J. P. <i>et al</i> , J. Med.Chem., 2001; 44, 1, 94-104)	MS(ES+) m/e 329 [M+H] <sup>+</sup>
223	4-(1-Ethyl-7-(((S)-1-pyrrolidin-2-ylmethyl)-amino)-methyl)-1 <i>H</i> -imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine	(S)-2-Aminomethyl-pyrrolidine-1-carboxylic acid <i>tert</i> -butyl ester (Slaitas, A. <i>et al</i> , Nucleosides Nucleotides, 2001; 20, 4-7, 1377-1380)	MS(ES+) m/e 343 [M+H] <sup>+</sup>
224	4-(7-((4-Aminomethyl-cyclohexylmethyl)-	(4-Aminomethyl-cyclohexylmethyl)-	MS(ES+) m/e 385 [M+H] <sup>+</sup>

	amino]-methyl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl)-furazan-3-ylamine	carbamic acid <i>tert</i> -butyl ester (Lum, R. T., WO 9532945)	
225	4-{1-Ethyl-7-[(2-piperazin-1-yl-ethylamino)-methyl]-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl)-furazan-3-ylamine	4-(2-Amino-ethyl)-piperazine-1-carboxylic acid <i>tert</i> -butyl ester (Krapcho, A. <i>et al</i> , J. Med.Chem., 1998; 41, 27, 5429-5444)	MS(ES+) m/e 372 [M+H] <sup>+</sup>
226	4-[7-((R)-3-Aminopyrrolidin-1-ylmethyl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl)furazan-3-ylamine	(3 <i>R</i> )-(+)-(3- <i>tert</i> -butoxycarbonylamino)pyrrolidine	MS(ES+) m/e 329 [M+H] <sup>+</sup>
227	4-[7-((S)-3-Aminopyrrolidin-1-ylmethyl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl)furazan-3-ylamine	(3 <i>S</i> )-(-)-(3- <i>tert</i> -butoxycarbonylamino)pyrrolidine	MS(ES+) m/e 329 [M+H] <sup>+</sup>
228	4-(1-Ethyl-7-[[[(pyrrolidin-2-ylmethyl)amino]methyl]-1 <i>H</i> -imidazo[4,5-	2-(Aminomethyl)-1- <i>N-tert</i> -butoxycarbonylpyrrolidine	MS(ES+) m/e 343 [M+H] <sup>+</sup>

	c]pyridin-2-yl)furazan-3-ylamine		
229	[2-(4-Aminofurazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ] ]pyridin-7-ylmethyl]methylpiperidin-4-yl-amine	1- <i>tert</i> -Butoxycarbonyl-4-methylaminopiperidine	MS(ES+) m/e 357 [M+H] <sup>+</sup>
230	{1-[2-(4-Aminofurazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ] pyridin-7-ylmethyl]piperidin-4-yl}methylamine	4-[N-( <i>tert</i> -butoxycarbonyl)-methylamino]piperidine (Russell <i>et al</i> , J. Med.Chem. 1999; 42;24, 4981-5001)	MS(ES+) m/e 357 [M+H] <sup>+</sup>
231	4-(7-[1,4]Diazepan-1-ylmethyl-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl)-furazan-3-ylamine	<i>tert</i> -butyl 1-homopiperazine carboxylate	MS(ES+) m/e 343 [M+H] <sup>+</sup>
232	4-(1-Ethyl-7-[[piperidin-4-ylmethyl)-amino]-methyl]-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-2-yl)furazan-3-yl amine	4-(aminomethyl)-1-boc-piperidine	MS(ES+) m/e 357 [M+H] <sup>+</sup>
233	N-[2-(4-aminofurazan-3-yl)-1-ethyl-1 <i>H</i> -	<i>trans</i> -(4-Amino-cyclohexyl)-	MS(ES+) m/e 357 [M+H] <sup>+</sup>

	imidazo[4,5-c]pyridin-7-methyl]- <i>trans</i> -cyclohexane-1,4-diamine	carbamic acid <i>tert</i> -butyl ester ( <i>Bioorganic &amp; Medicinal Chemistry</i> (2000), 8(6), 1451)	
234	{1-[2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-ylmethyl]-piperidin-4-yl}-methyl-amine	<i>N</i> -Methyl-piperidin-4-yl-carbamic acid <i>tert</i> -butyl ester	MS(ES+) m/e 357 [M+H] <sup>+</sup>
235	4-{1-Ethyl-7-[(2-piperazin-1-yl-ethylamino)-methyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine	4-(2-Amino-ethyl)-piperazine-1-carboxylic acid <i>tert</i> -butyl ester (Krapcho <i>et al</i> , J. Med.Chem., 1998; 41; 27, 5429-5444)	MS(ES+) m/e 372 [M+H] <sup>+</sup>

**Example 236:** {1-[2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-ylmethyl]-piperidin-4-yl}-cyclopropyl-amine



**Step 1: 4-[7-(1,4-Dioxo-8-aza-spiro[4.5]dec-8-ylmethyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine**

The title compound was prepared from the product of Example 191, Step 1 and 4-piperidone-ethylene-ketal using the method of Example 200. MS(ES+) m/e 386 [M+H]<sup>+</sup>.

5

**Step 2: 1-[2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-ylmethyl]-piperidin-4-one**

The product from Step 1 (0.245g, 0.64mmole) in 1,4-dioxane (20ml) and aqueous hydrochloric acid (5M, 10ml) was heated under reflux for 18 hours. The mixture was allowed to cool to ambient temperature, neutralised by addition of aqueous sodium hydroxide solution (5M) and extracted into dichloromethane.

10

The combined organic extracts were dried under magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with ethyl acetate to afford the title compound (0.054g); MS(ES+) m/e 341 [M+H]<sup>+</sup>.

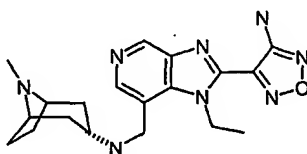
15

**Step 3: {1-[2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-ylmethyl]-piperidin-4-yl}-cyclopropyl-amine**

The title compound was prepared from the product of Step 2 and cyclopropylamine using the method of Example 200. MS(ES+) m/e 383 [M+H]<sup>+</sup>.

20

**Example 237. [2-(4-Amino-furazan-3-yl)-1-ethyl-1-H-imidazo [4,5-c]pyridin-7-ylmethyl]-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-amine dihydrochloride**



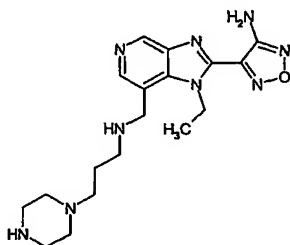
The product of Example 191 Step 1 (150mg, 0.58mmole) in 5% acetic acid and

25 dichloromethane (5ml) was treated with 8-Methyl-8-aza-bicyclo[3.2.1]oct-3-ylamine (179mg,



1.2mmole) and stirred at ambient temperature for 20 minutes. Sodium borohydride (13mg, 0.34mmol) was added and the reaction mixture stirred at ambient temperature for 20 hours. The product was diluted with dichloromethane, washed water followed by saturated brine, dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 20% ammonia in methanol / dichloromethane. to afford the title compound as a free base; (34mg, 15%) MS(ES<sup>+</sup>) m/e 396 [M+H]<sup>+</sup>. A solution of the resulting free base (34mg, 0.08mmol) in anhydrous methanol (1ml) was treated with 1M hydrochloric acid in ether and stirred for 30 minutes. The resulting white precipitate was filtered and dried *in vacuo* to afford the title compound as a colourless hydrochloride salt; (34mg, 92%) MS (ES<sup>+</sup>) m/e 396 [M+H]<sup>+</sup>.

**Example 238: 4-{1-Ethyl-7-[(3-piperazin-1-yl-propylamino)-methyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furan-3-ylamine**



**Step 1: (3-Oxo-propyl)-carbamic acid *tert*-butyl ester**

A solution of oxalyl chloride (0.27ml, 3.15mmole) in dry dichloromethane (8ml) was cooled to -78°C. Dimethyl sulfoxide (0.45ml, 6.29mmole) in dichloromethane (1ml) was added dropwise maintaining the reaction temperature at -40°C. The reaction mixture was stirred for 5 minutes and a solution of (3-hydroxy-propyl)-carbamic acid *tert*-butyl ester (0.50g, 2.86mmole) in dichloromethane (3ml) was added dropwise. After stirring for 15 minutes, triethylamine (1.99ml, 14.3 mmole) was added and the mixture allowed to warm to ambient temperature. The reaction was quenched by adding water (10ml), extracted with dichloromethane and the organic extracts were washed with aqueous hydrochloric acid

solution (2M), saturated sodium bicarbonate solution and water. The organic layer was dried under magnesium sulfate and the solvent removed in vacuo to afford the title compound (0.45g). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.81 (1H, s), 3.45-3.40 (2H, t, J 5Hz), 2.72-2.69 (2H, t, J 5Hz), 1.43 (9H, s).

5

**Step 2: 4-(3-*tert*-Butoxycarbonylamino-propyl)-piperazine-1-carboxylic acid 9 *H*-fluoren-9-ylmethyl ester**

Piperazine-1-carboxylic acid 9 *H*-fluoren-9-ylmethyl ester hydrochloride (0.67g, 1.93mmole) was dissolved in methanol (5ml), treated with diisopropylamine (0.34ml, 1.93mmole) and allowed to stir at room temperature for 5 minutes. The product from Step 1 (0.50g, 2.89mmole) and sodium cyanoborohydride (133mg, 2.12mmole) were added and the mixture stirred under argon for 18 hours. The solvent was removed in vacuo and the residue was dissolved in dichloromethane, washed with saturated sodium bicarbonate solution, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography eluting with ethyl acetate/hexane (1:1) to afford the title compound (0.71g). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.78-7.75 (2H, d), 7.59-7.56 (2H, d), 7.41-7.31 (4H, m), 4.52-4.43 (2H, d), 4.27-4.20 (1H, t), 3.51-3.42 (4H, br m), 3.25-3.15 (2H, m), 2.45-2.35 (6H, m), 1.72-1.60 (2H, m), 1.45 (9H, s).

**Step 3: 4-(3-Amino-propyl)-piperazine-1-carboxylic acid 9 *H*-fluoren-9-ylmethyl ester**

The title compound was obtained from the product of step 2 by the general method of Example 21. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.78-7.75 (2H, d), 7.60-7.55 (2H, d), 7.40-7.31 (4H, m), 4.48-4.44 (2H, d), 4.26-4.20 (1H, t), 3.50-3.41 (4H, br m), 3.01-2.94 (2H, m), 2.58-2.50 (2H, m), 2.45-2.40 (4H, br m), 1.80-1.75 (2H, m).

25

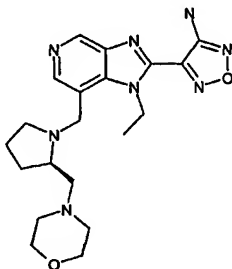
**Step 4: 4-(3-([2-(4-Amino-furazan-3-yl)-1-ethyl-1 *H*-imidazo[4,5-*c*]pyridin-7-ylmethyl]-amino)-propyl)-piperazine-1-carboxylic acid 9 *H*-fluoren-9-ylmethyl ester**

The title compound was prepared from the product of Example 191 Step 1 and the product from Step 3 using the method of Example 200. MS(ES+) m/e 608 [M+H]<sup>+</sup>.

**Step 5: 4-{1-Ethyl-7-[(3-piperazin-1-yl-propylamino)-methyl]-1H-imidazo[4,5-c]pyridin-2-yl}-furazan-3-ylamine**

The product from step 4 (0.17g, 0.28mmole) was dissolved in dichloromethane (3ml) and treated with piperidine (0.3ml, 2.8mmole). The mixture was stirred at room temperature under argon for 4 hours. The solvent was removed in vacuo and the residue purified by column chromatography on silica gel eluting with ammonia/methanol/dichloromethane (1:9:90) to afford the title compound (0.063g). MS(ES+) m/e 386 [M+H]<sup>+</sup>.

**Example 239: 4-[1-Ethyl-7-((R)-2-morpholin-4-ylmethyl-pyrrolidin-1-ylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine**



**Step 1: (R)-2-Morpholin-4-ylmethyl-pyrrolidine-1-carboxylic acid tert-butyl ester**

The title compound was prepared from N-(t-butoxycarbonyl)D-prolinal and morpholine according to the general method of Example 200; MS (ES+), m/e 271 [M+H]<sup>+</sup>.

**Step 2: 4-(R)-1-Pyrrolidin-2-ylmethyl-morpholine**

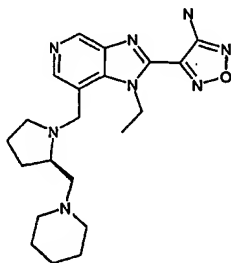
The title compound was prepared from the product of step 1 according to the general method of Example 191 Step 3; MS (ES+), m/e 171 [M+H]<sup>+</sup>.

**Step 3: 4-[1-Ethyl-7-((R)-2-morpholin-4-ylmethyl-pyrrolidin-1-ylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine**

The title compound was prepared from the product of Step 2 and the product of Example 191 Step 1 using the procedures detailed in example 200; MS (ES<sup>+</sup>), m/e 413 [M+H]<sup>+</sup>.

5

**Example 240: 4-[1-Ethyl-7-((R)-2-piperidin-1-ylmethyl-pyrrolidin-1-ylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine**



**Step 1 : (R)-2-Piperidin-1-ylmethyl-pyrrolidine-1-carboxylic acid tert-butyl ester**

- 10 The title compound was prepared from N-(t-butoxycarbonyl)D-prolinal and piperidine using the procedure detailed in example 200; MS (ES<sup>+</sup>), m/e 269 [M+H]<sup>+</sup>.

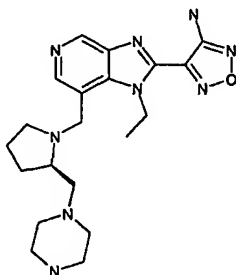
**Step 2: 1-(R)-1-Pyrrolidin-2-ylmethyl-piperidine**

- 15 The title compound was prepared from the product of step 1 using the procedure detailed in Example 191 step 3; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 3.24 (1H, m), 2.96 (1H, m), 2.82 (1H, m), 2.45 (2H, m), 2.33-2.24 (4H, m), 1.95 (2H, br s), 1.85 (1H, m), 1.73 (2H, m), 1.57 (3H, m), 1.41 (2H, m), 1.31 (1H, m).

- 20 **Step 3: 4-[1-Ethyl-7-((R)-2-piperidin-1-ylmethyl-pyrrolidin-1-ylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine**

The title compound was prepared from the product of Step 2 and the product of Example 191 Step 1, using the general procedure of Example 200; MS (ES<sup>+</sup>), m/e 411 [M+H]<sup>+</sup>.

**Example 241: 4-[1-Ethyl-7-((R)-2-piperazin-1-ylmethyl-cyclopentylmethyl)-1 H -imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine**



**5 Step 1 : 4-(R)-1-Pyrrolidin-2-ylmethyl-piperazine-1-carboxylic acid 9 H-fluoren-9-ylmethyl ester trifluoroacetate**

To a solution of piperazine carboxylic acid 9-fluorenylmethyl ester hydrochloride (690mg, 2mmol), in dichloromethane was added diisopropylethylamine (258mg, 2mmol) followed by N(t-butoxycarbonyl)D-prolinal (400mg, 2mmol) and the resulting solution was stirred for 10 minutes, and treated with sodium triacetoxyborohydride (850mg, 4mmol) and stirred for 4 hours at room temperature. The reaction was diluted with water and extracted with dichloromethane at pH 7. The combined organic phase was dried over anhydrous sodium sulfate. The dichloromethane solution was then treated with trifluoroacetic acid (5ml) and stirred for 16 hours at room temperature. The solvent was evaporated in vacuo to afford the title compound; MS (ES<sup>+</sup>), m/e 392 [M+H]<sup>+</sup>.

**Step 2: 4-[1-Ethyl-7-((R)-2-piperazin-1-ylmethyl-cyclopentylmethyl)-1 H -imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine**

The product of example 191 step 1 (100mg, 0.387mmol) was dissolved in 1,2-dichloroethane (2.5ml) and added to a stirred solution of the product of Step 1 (480mg, 0.774mmol) and diisopropyl ethylamine (100mg, 0.774mmol) in 1,2-dichloroethane (2.5ml). After stirring for 5 minutes the reaction was treated with sodium triacetoxyborohydride (164mg, 0.774mmol)

and the reaction was stirred for 16 hours at room temperature. The reaction was then treated with piperidine (5ml) and stirred for 5 hours at room temperature. The solvent was then evaporated *in vacuo* and the residue diluted with dichloromethane, washed with saturated sodium bicarbonate solution, water, brine, dried over anhydrous sodium sulfate and

5 evaporated *in vacuo*. The residue was purified by automated reverse phase chromatography (Biotage flex, acetonitrile/water eluant) to afford the title compound (30mg, 19%); MS (ES+), m/e 412 [M+H]<sup>+</sup>.

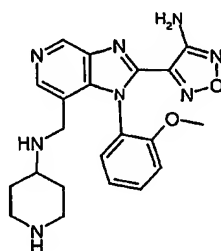
The following compounds were prepared by the general method of Example 200 using

10 starting materials indicated.

	Example	Aldehyde from Example #	Amine	Characterisation
242	4-[1-Ethyl-7-(4-phenylaminomethyl-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	191	Aniline	MS (ES+) m/e 412 [M+H] <sup>+</sup>
243	4-[1-Ethyl-7-(4-fluoro-3-pyrrolidin-1-ylmethyl-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine	113	Pyrrolidine	MS (ES+) m/e 408 [M+H] <sup>+</sup>
244	4-[1-Ethyl-7-(3-fluoro-4-pyrrolidin-1-ylmethyl-phenyl)-1H-imidazo[4,5-	119	Pyrrolidine	MS (ES+) m/e 408 [M+H] <sup>+</sup>

	c]pyridin-2-yl]-furan-3-ylamine			
245	4-[1-Ethyl-7-(4-ethylaminomethyl-3-fluoro-phenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furan-3-ylamine	119	Ethylamine	MS (ES+) m/e 382 [M+H] <sup>+</sup>

**Example 246:** (2-Furan-3-yl-3-(2-methoxy-phenyl)-3-H-pyrrolo(2,3-c)pyridin-4-ylmethyl)-piperidin-4-yl-amine.



**5 Step 1. (2-Bromo-6-nitro-pyridyl)-(2-methoxy-phenyl)-amine**

The title compound was prepared from the product of Example 177, Step 2 and 1-amino-2-methoxybenzene by the general method of Example 25 Step 1. MS (ES+) m/e 324 [M+H]<sup>+</sup>.

**Step 2. 5-Bromo-N<sup>4</sup>-(2-methoxy-phenyl)-pyridine-3,4-diamine**

- 10 A solution of the product of Step 1 (1g, 3.08mmol) in ethanol (11ml) / water (2.5ml) / conc.HCl (1ml) was stirred at 0°C and iron filings (1g, 18.5mmol) were added portionwise. The mixture was warmed to room temperature and stirred for 18 hours. The mixture was poured onto ice water (100ml) and basified using 1M sodium carbonate solution. The resulting mixture was filtered through kieselgel and the pad was washed copiously with

ethanol. The organic phase was removed *in vacuo* to leave an orange emulsion, this was extracted into ethyl acetate, washed with water (x3), dried using magnesium sulphate and evaporated *in vacuo*. Purification of the residue by silica gel chromatography eluting with 2% methanol in dichloromethane afforded the title compound (500mg, 45%). MS (ES+) m/e 293 [M+H]<sup>+</sup>.

**Step 3. 4-(7-bromo-1-(2-methoxy-phenyl)-1 H-imidazo(4,5-c)pyridin-2-yl)-furazan-3-ylamine**

The title compound was obtained from the product of Step 2 by the general method of

Example 1 Steps 3 and 4; MS (ES+) m/e 387 [M+H]<sup>+</sup>.

**Step 4. 2-(4-Amino-furazan-3-yl)-1-(2-methoxy-phenyl)-1 H-imidazo(4,5-c) pyridine-7-carbaldehyde.**

The title compound was prepared from the product of Step 3 by the general method of

Example 191 Step 1; MS (ES+) m/e 337 [M+H]<sup>+</sup>.

**Step 5. 4-((2-(4-Amino-furazan-3-yl)-3-(2-methoxy-phenyl)-3 H-pyrrolo(2,3-c) pyridin-4-ylmethyl)-amino)-piperidine-1-carboxylic acid *tert* butyl ester**

The title compound was obtained from the product of Step 4 and 4-aminopiperidine-1-carboxylic acid *tert* butyl ester by the general method of Example 200; MS (ES+) m/e 520 [M+H]<sup>+</sup>.

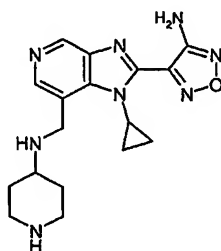
**Step 6. (2-Furazan-3-yl-3-(2-methoxy-phenyl)-3-H-pyrrolo(2,3-c)pyridin-4-ylmethyl)-piperidin-4-yl-amine**

The product of step 5 was treated according to the general method of Example 191 Step 3. A solution of the resulting free base (12mg, 0.03mmol) in anhydrous methanol (0.5ml) was treated with 1M hydrochloric acid in ether and stirred for 30 minutes. The resulting white



precipitate was filtered and dried *in vacuo* to afford the title compound as a colourless solid (12mg, 63%); MS (ES+) m/e 420 [M+H]<sup>+</sup>.

**Example 247: (3-Cyclopropyl-2-furazan-3-yl-3 *H*-pyrrolo(2,3-*c*) pyridin-4-ylmethyl)-piperidin-4-yl-amine dihydrochloride**



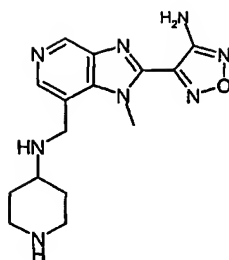
The title compound was prepared from the product of Example 177 Step 3 using the methods of Example 246 Steps 2-6; MS (AP+) m/e 354 [M+H]<sup>+</sup>.

The following example was prepared by the general method described in Example

247.

	Example	Amine (C-7)	Characterisation
248	<p>4-(1-Cyclopropyl-7-piperazin-1-ylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl-furazan-3-ylamine</p>	<p>piperazine-1-carboxylic acid <i>tert</i>-butyl ester</p>	<p>MS(AP+) m/e 340 [M+H]<sup>+</sup></p>

**Example 249: [2-(4-Amino-furazan-3-yl)-1-methyl-1*H*-imidazo[4,5-*c*]pyridin-7-ylmethyl]-piperidin-4-yl-amine**



**Step 1: N-(2-Bromo-6-nitro-pyridyl)-methanamine**

The title compound was prepared from 3-bromo-4-chloro-5-nitropyridine and methanamine by the general method of Example 246 Step 1. MS (ES+) m/e 329 [M+H]<sup>+</sup>.

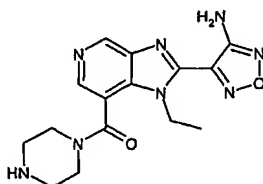
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**Step 2: [2-(4-Amino-furazan-3-yl)-1-methyl-1H-imidazo[4,5-c]pyridin-7-ylmethyl]-piperidin-4-yl-amine**

The title compound was prepared from the product of Step 1 using the methods of Example 246 Steps 2-6; MS (ES+) m/e 328 [M+H]<sup>+</sup>.

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**Example 250 . 1-[2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]-1-piperazin-1-yl-methanone dihydrochloride**



**Step 1. 2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid**

A solution of the product from Example 100 (5g, 18.25mmol) in tetrahydrofuran (200ml) at -78°C was treated with a 2M solution lithium diisopropylamide (LDA, 18ml, 36.5mmol) in hexanes under argon. After 5 minutes the solution was treated with a 1.6M solution of n-butyl lithium (34ml, 54.7mmol) in hexanes at -78°C. The mixture was stirred for 10mins, then carbon dioxide gas was bubbled through the solution for 10mins. The resulting pale yellow

20

suspension was allowed to warm to room temperature over 2h, water (10ml) in tetrahydrofuran (30ml) was cautiously added dropwise and the mixture concentrated *in vacuo*. The residual solid was washed with ether (2x100ml) then dissolved in methanol (100ml) containing glacial acetic acid. The solvent was evaporated and the residue triturated under ether (50ml) and filtered to give the title compound as a buff coloured solid (3.28, 74%); MS (ES+) m/e 275 [M+H]<sup>+</sup>.

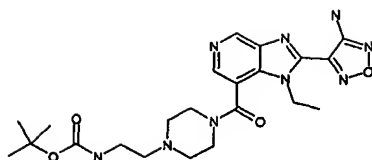
**Step 2. 4-{1-[2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo [4,5-*c*]pyridin-7-yl]-methanoyl}-piperazine-1-carboxylic acid, *tert*-butyl ester.**

1,1'-Carbonyldiimidazole (177mg) was added to a solution of the product from Step 1 (0.1g, 0.36mmol) in dry DMF (5ml) at room temperature under argon. The mixture was stirred for 18h, then *tert*-butyl -1-piperazine carboxylate added. The mixture was stirred at room temperature for 16h, then partitioned between water (15ml) and ethyl acetate (3x15ml). The combined organic extracts were washed with brine (2x20ml), dried over anhydrous sodium sulphate, filtered and evaporated. The residue was purified by silica gel chromatography eluting with dichloromethane / ethanol / ammonia 300:8:1, to afford the title compound, (0.064g, 40%); MS (ES+) m/e 443 [M+H]<sup>+</sup>.

**Step3 . 1-[2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-7-yl]-1-piperazin-1-yl-methanone. dihydrochloride**

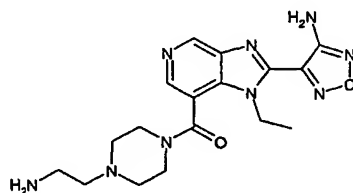
Ethereal hydrogen chloride (1.0M; 1ml) was added to a solution of the product from Step 2 (0.064g, 0.15mmol) in methanol (1ml) at room temperature under argon. The mixture was stirred for 16h, the solvent was evaporated and the residue triturated under ether to give the title compound as a colourless solid (0.047, 79%); MS (ES+) m/e 343 [M+H]<sup>+</sup>.

**Example 251. [2-(4-{1-[2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-7-yl]-methanoyl}-piperizin-1-yl)-ethyl]-carbamic acid *tert*-butyl ester.**



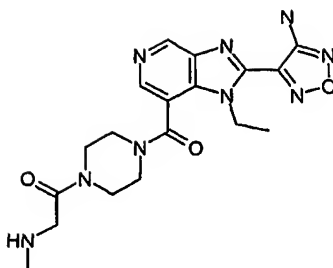
A mixture of the free base from Example 250, Step 3 (prepared by eluting a sample of the dihydrochloride salt through an SCX cartridge using ammonia (10%) in ethanol) and tert-butyl N-(2-oxoethyl)carbamate (0.065g, 0.41mmol) in 1,2-dichloroethane (5ml) was stirred at room temperature for 20 mins. This was then treated according to the method of Example 200 to afford the title compound; MS (ES+) m/e 486 [M+H]<sup>+</sup>.

**Example 252. [1-[4-(2Amino-ethyl)-piperizin-1-yl]-1-[2-(4-amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yl]-methanone. Dihydrochloride**



Ethereal hydrogen chloride (1.0M; 1ml) was added to a solution of the product from example 251 (0.042g, 0.086mmol) in methanol (2ml) and the solution stirred at room temperature for 16h. The solvent was evaporated and the residual solid triturated under ether (10ml) and filtered to give the title compound as a colourless solid (0.039g, 99%); MS (ES+) m/e 386 [M+H]<sup>+</sup>.

**Example 253. 1-(4-{1-[2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo [4,5- c] pyridin-7-yl]-methanoyl}-piperazin-1-yl)-2-methylamino-ethanone**



**Step 1. [2-(4-{1-[2-(4-Amino-furazan-3-yl)-1-ethyl-1 H -imidazo [4,5-c]pyridin-7-yl]-methanoyl}-piperazin-1-yl)-2-oxo-ethyl]-methyl-carbamic acid *tert*-butyl ester**

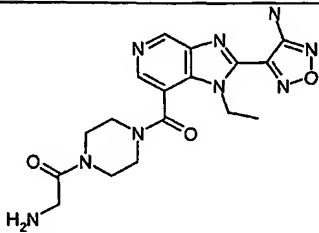
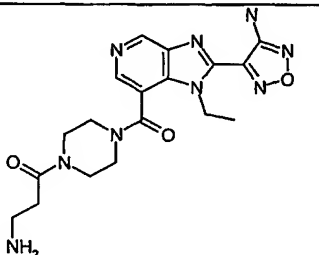
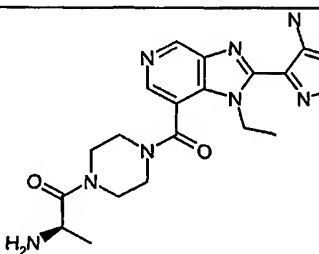
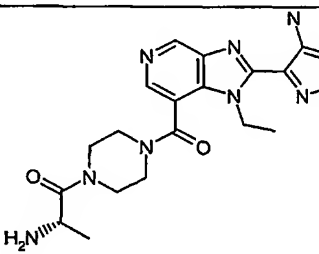
- 5 N-cyclohexylcarbodiimide, N-methyl polystyrene HL (1.69mmol/g; 515mg, 0.88mmol) in dichloromethane ( 2ml ) was treated with Boc-Sarcosine (83mg, 0.44mmol), followed by HOBT (59mg, 0.44mmol). The mixture was stirred for 10 minutes, then treated with the title compound from Example 250 ( 75mg, 0.22mmol) in triethylamine (92ul, 0.66mmol) and dichloromethane (1ml ). The reaction mixture was stirred for 2 hours, then passed down an
- 10 SCX cartridge eluting methanol the 10% ammonia methanol to afford the title compound (105mg, 70%) MS (ES+) m/e 513 [M+H]<sup>+</sup>.

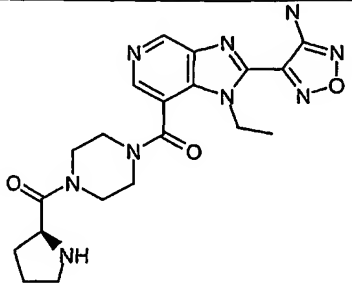
**Step 2. 1-(4-{1-[2-(4-Amino-furazan-3-yl)-1-ethyl-1 H -imidazo [4,5- c] pyridin-7-yl]-methanoyl}-piperazin-1-yl)-2-methylamino-ethanone**

15

The product of step 1 ( 105mg, 0.2mmol) was dissolved in DCM (2ml) and hydrochloric acid in ether (1M, 10 equiv.) was added. The mixture was stirred for 16 hours and the resulting white precipitate was filtered and dried *in vacuo* to afford the title compound as a colourless solid (44mg, 52%); MS (ES+) m/e 413 [M+H]<sup>+</sup>.

- 20 The following examples were prepared from the product of Example 250. Using the two-step method described in Example 253 Steps 1 and 2.

	Example	Acid	Characterisation
254	 The structure shows a 4-ethyl-7-oxo-5,6,7,8-tetrahydro-1H-benzotriazin-2-yl group attached to a piperidine ring via a carbonyl group. The piperidine ring is also attached to a carbonyl group, which is further attached to a glycine moiety (CH2NH2).	Boc- Glycine	MS(ES+) m/e 399 [M+H] <sup>+</sup>
255	 The structure is similar to the one in Example 254, but the glycine moiety is replaced by a beta-alanine moiety (CH2CH2NH2).	Boc-Beta-L-alanine	MS(ES+) m/e 413 [M+H] <sup>+</sup>
256	 The structure is similar to the one in Example 254, but the glycine moiety is replaced by an L-alanine moiety (CH(CH3)NH2).	Boc-L-alanine	MS(ES+) m/e 413 [M+H] <sup>+</sup>
257	 The structure is similar to the one in Example 254, but the glycine moiety is replaced by a D-alanine moiety (CH(CH3)NH2, with the methyl group on a wedge).	Boc-D-alanine	MS(ES+) m/e 413 [M+H] <sup>+</sup>

258	 <p>The chemical structure shows a Boc-L-proline moiety (a five-membered ring with an NH group and a tert-butyl ester group) linked via a piperidine ring to a pyridine ring. The pyridine ring is further substituted with an imidazo-furazan system.</p>	Boc-L-proline	MS(ES+) m/e 439 [M+H] <sup>+</sup>
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The following examples were prepared from the product of Example 250 Step 1 using the two-step method described in example 250 Steps 2 and 3

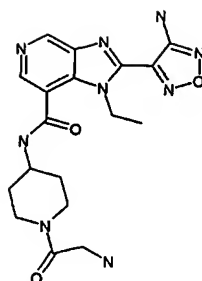
	Example	Amine	Characterisation
259	2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridine-7-carboxylic acid (piperidin-4-yl methyl)-amide dihydrochloride	4-Aminomethyl piperidin-1-carboxylic acid <i>tert</i> -butyl ester	MS(ES+) m/e 371 [M+H] <sup>+</sup>
260	(±) 2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridine-7-carboxylic acid (piperidin-3-ylamide dihydrochloride	(±)-3-Amino piperidine-1-carboxylic acid <i>tert</i> -butyl ester	MS(ES+) m/e 357 [M+H] <sup>+</sup>
261	2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridine-7-carboxylic acid piperidin-4-ylamide dihydrochloride	4-Amino-piperidine-1-carboxylic acid <i>tert</i> -butyl ester	MS(ES+) m/e 357 [M+H] <sup>+</sup>
262	2-(4-Amino-furazan-3-yl)-1-	(3-Amino-propyl)-	MS(ES+) m/e 345

	ethyl-1 <i>H</i> -imidazo[4,5- c]pyridine-7-carboxylic acid (3- methylamino-propyl)- amide dihydrochloride	methyl-carbamic acid <i>tert</i> -butyl ester	[M+H] <sup>+</sup>
263	2-(4-Amino-furazan-3-yl)-1- ethyl-1 <i>H</i> -imidazo[4,5- c]pyridine-7-carboxylic acid (4- amino-butyl)- amide dihydrochloride	(4-Amino-butyl)- carbamic acid <i>tert</i> butyl ester	MS(ES+) m/e 345 [M+H] <sup>+</sup>
264	2-(4-Amino-furazan-3-yl)-1- ethyl-1 <i>H</i> -imidazo[4,5- c]pyridine-7-carboxylic acid (6- amino-hexyl)- amide dihydrochloride	(6-Amino-hexyl)- carbamic acid <i>tert</i> butyl ester	MS(ES+) m/e 373 [M+H] <sup>+</sup>
265	(+/-)-2-(4-Amino-furazan-3-yl)- 1-ethyl-1 <i>H</i> -imidazo[4,5- c]pyridine-7-carboxylic acid (piperidin-2-yl methyl)-amide dihydrochloride	2-Aminomethyl- piperidine-1- carboxylic acid <i>tert</i> - butyl ester	MS(ES+) m/e 471 [M+H] <sup>+</sup>
266	1-[2-(4-Amino-furazan-3-yl)-1- ethyl-1 <i>H</i> -imidazo[4,5- c]pyridine-7-yl]-1-(( <i>R</i> )-3-amino- pyrrolidin-1-yl)-methanone dihydrochloride	( <i>R</i> )-Pyrrolidin-3-yl- carbamic acid <i>tert</i> - butyl ester	MS(ES+) m/e 343 [M+H] <sup>+</sup> [α] <sub>D</sub> (27.6)C = -3.34 (c= 2.75%, DMF)
267	1-[2-(4-Amino-furazan-3-yl)-1- ethyl-1 <i>H</i> -imidazo[4,5-	( <i>S</i> )-Pyrrolidin-3-yl- carbamic acid <i>tert</i> -	MS(ES+) m/e 343 [M+H] <sup>+</sup>



	c]pyridine-7-yl]-1-((S)-3-amino-pyrrolidin-1-yl)-methanone dihydrochloride	butyl ester	[ $\alpha$ ] <sub>D</sub> (27.2)C = +1.31 (c= 3.75%, DMF)
268	2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5-c]pyridine-7-carboxylic acid (R)-pyrrolidin-3-ylamide dihydrochloride	(R)-3-Amino-pyrrolidine-1-carboxylic acid tert-butyl ester	MS(ES+) m/e 343 [M+H] <sup>+</sup>
269	2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5-c]pyridine-7-carboxylic acid (S)-pyrrolidin-3-ylamide dihydrochloride	(S)-3-Amino-pyrrolidine-1-carboxylic acid tert-butyl ester	MS(ES+) m/e 343 [M+H] <sup>+</sup>
270	2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5-c]pyridine-7-carboxylic acid (morpholin-2-ylmethyl)-amide dihydrochloride	2-Aminomethyl-morpholine-4-carboxylic acid tert-butyl ester	MS(ES+) m/e 373 [M+H] <sup>+</sup>

**Example 271. 2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-c]pyridine- 7-carboxylic acid[1-(2-amino-ethanoyl)-piperidine-4-yl]-amide dihydrochloride**



**Step 1. 2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-yl-methanoyl-(2-amino-ethanoyl)-piperidine-4-yl-amide dihydrochloride**

- 5 A mixture of N-cyclohexylcarbodiimide, N-methyl polystyrene HL (1.69mmol/g; 300mg, 0.507mmol) and tert-butoxycarbonylamino-acetic acid (82mg, 0.466mmol) in dry dichloromethane (3ml) was stirred for 10 mins at room temperature under argon. 1-hydroxybenzotriazole hydrate (HOBt; 71mg 0.466mmol) was added and the mixture stirred for a further 10 mins. A solution of the product from example 261 (0.1g, 0.233mmol) and triethylamine (0.1ml, 0.507mmol) in dry DMF (3ml) was added and the mixture stirred for 16h. The mixture was then applied to a SCX ion exchange column, eluted with methanol and then a mixture of methanol/0.880 ammonia (9:1). The basic fractions were then evaporated and the residual solid triturated under ether and filtered to afford the title compound, (0.067g, 56%); MS (ES+) m/e 514 [M+H]<sup>+</sup>.

**Step2 . 2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid[1-(2-amino-ethanoyl)-piperidine-4-yl]-amide dihydrochloride**

- Ethereal hydrogen chloride (1.0M; 2ml) was added to a solution of the product from Step 1 (0.067g, 0.13mmol) in methanol (3ml) at room temperature under argon. The mixture was stirred for 16h, the solvent was evaporated and the residue triturated under ether to give the title compound as a colourless solid (0.058, 79%); MS (ES+) m/e 414 [M+H]<sup>+</sup>.

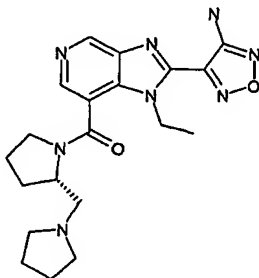
The following examples were prepared from the product of Example 261 using the two-step method described in Example 271 Step 1

	Example	Acid	Characterisation
272	2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridine-7-carboxylic acid [1-(3-amino-propanoyl)-piperidin-4-yl]-amide dihydrochloride	3-Amino-propionic acid	MS(ES+) <i>m/e</i> 428 [M+H] <sup>+</sup>
273	2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridine-7-carboxylic acid [1-(( <i>s</i> )-1-pyrrolidin-2-yl-methanoyl)-piperidin-4-yl]-amide dihydrochloride	( <i>S</i> )-Pyrrolidine – 2-carboxylic acid	MS(ES+) <i>m/e</i> 454 [M+H] <sup>+</sup>

5 The following examples were prepared from the product of Example 250 Step 1 using the method described in example 250 Step 2

	Example	Amine	Characterisation
274	1-[2-(4-Amino-furazan-3-yl)-1-ethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]pyridin-7-yl]-1-pyrrolidin-1-yl-methanone	pyrrolidine	MS(ES+) <i>m/e</i> 328 [M+H] <sup>+</sup>

**Example 275. 1-[2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo [4,5-*c*]pyridin-7-yl]-1-((*S*)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone dihydrochloride**



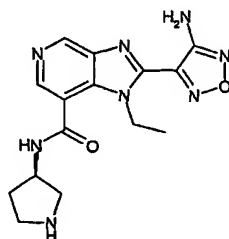
**Step 1 1-[2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo [4,5-*c*]pyridin-7-yl]-1-imidazol-1-yl-methanone**

1,1'-Carbonyldiimidazole (0.89g) was added to a solution of the product from Example 250 Step 1 (0.5g, 1.82mmol) in dry DMF (10ml) at room temperature under argon. The mixture was stirred for 18h resulting in the precipitation of a colourless solid. Ether (10ml) was added and the solid filtered to give the title compound, (0.5g, 85%); MS (ES+) *m/e* 325 [M+H]<sup>+</sup>.

**Step 2 1-[2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo [4,5-*c*]pyridin-7-yl]-1-((*S*)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone**

A mixture of (*S*)(+)-1-(2-pyrrolidinylmethyl)pyrrolidine (0.142g; 0.93mmol) and the product from Step 1 (0.1g; 0.31mmol) in DMF (2ml) was warmed at 60°C for 18h. The cooled mixture was partitioned between water (10ml) and ethyl acetate (3x10ml). The combined organic extracts were washed with brine (2x20ml), dried over anhydrous sodium sulphate, filtered and evaporated to give a colourless gum. The crude material was purified by preparative HPLC using Dynamax C18 column, 8 micron particle size; 250 mm x 41.4 mm i.d.; 10-90% acetonitrile / water (0.1%TFA);70 ml/min; UV detection at 254 nm) to afford the title compound, (0.055g, 28%); MS (ES+) *m/e* 411 [M+H]<sup>+</sup>.

**Example 276. 2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid (R)-pyrrolidin-3-yl amide**



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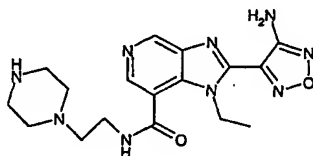
The product of Example 275 Step 1 (150mg) and (R)-3-amino-1-pyrrolidine-1-carboxylic acid *tert*-butyl ester (172 mg) were reacted according to the general method of Example 275, Step 2 followed by the general method described in example 250 step 3 to give the title compound; MS (ES+) *m/e* 443 [M+H]<sup>+</sup>.

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The following example was prepared by the general method described in Example 276

	Example	Amine	Characterisation
277	2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid (R)-pyrrolidin-3-yl amide	(R)-3-amino-1-pyrrolidine-1-carboxylic acid <i>tert</i> -butyl ester	MS (ES+) <i>m/e</i> 367 [M+H] <sup>+</sup>

**Example 278 2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid (2-piperizin-1-yl-ethyl)-amide dihydrochloride**



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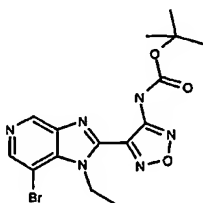
**Step 1. 4-[2-({1-[2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-yl]-methanoyl}-amino)-ethyl]-piperizin-1-carboxylic acid benzyl ester**

The product of Example 250 Step 1 and 4-(2-amino-ethyl)-piperazine-1-carboxylic acid benzyl ester were reacted according to the general method of Example 250, Step 2 to give  
5 the title compound; MS (ES+) m/e 520 [M+H]<sup>+</sup>.

**Step 2 2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid (2-piperizin-1-yl-ethyl)-amide dihydrochloride**

Hydrogen bromide (30% in acetic acid; 0.5ml) was added to a solution of the product from  
10 Step 1 (0.085g, 0.165mmol) in dry dichloromethane (5ml) at room temperature under argon. The mixture was stirred for 10 mins. resulting in the precipitation of a colourless solid which was filtered off, partitioned between sodium carbonate solution (2N, 5ml) and ethyl acetate (2x10ml). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), evaporated, dissolved in methanol (2ml) and ethereal HCl (1.0M; 0.5ml) added. The solvent was then evaporated  
15 and the residue triturated with ether (2ml) and filtered to give the title compound (16mg, 21%); MS (ES+) m/e 386 [M+H]<sup>+</sup>.

**Example 279. [4-(7-Bromo-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-yl]-carbamic acid *tert*-butyl ester**

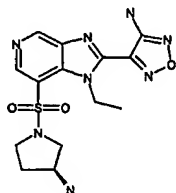


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A solution of the product from Example 100 (1.0g, 3.23mmol) in dichloroethane (5 mL) and pyridine (10 mL) was treated with DMAP (0.435g, 3.56mmol) and Boc<sub>2</sub>O (1.06g, 4.85mmol). The solution was heated to 70°C and was stirred overnight. The reaction is not complete, so

more DMAP (0.197g, 1.62mmol) and Boc<sub>2</sub>O (0.353g, 1.62mmol) were added, and the reaction mixture was stirred overnight. The reaction mixture was then cooled, and concentrated *in-vacuo*. The black residue was dissolved up in H<sub>2</sub>O and EtOAc, and the product was extracted into the organic layer. The layers were separated, and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give the pure product as a tan solid (1.25g, 95%); MS (ES+) *m/e* 410 [M+H]<sup>+</sup>.

**Example 280. 4-[7-((S)-3-Amino-pyrrolidine-1-sulfonyl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-furazan-3-ylamine**



**Step 1. {4-[7-((S)-3- *tert*-Butoxycarbonylamino-pyrrolidine-1-sulfonyl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-furazan-3-yl}-carbamic acid *tert*-butyl ester**

A solution of the product from Example 279 (0.150g, 0.367mmol) in tetrahydrofuran (2ml) at ambient temperature was treated with NaH (60%) under Argon. After 10 minutes, the mixture was cooled to -78°C, and was treated with *n*-butyllithium. After 10 minutes, the mixture was treated with a SO<sub>2</sub> solution (2mL), formed from bubbling SO<sub>2</sub> gas into THF (2mL). After 10 minutes of stirring, the mixture was treated with SO<sub>2</sub>Cl<sub>2</sub>, and was allowed to warm to ambient temperature. The reaction mixture was then concentrated, *in-vacuo*, to dryness. The solid was dissolved in dichloromethane (2.5mL) and pyridine (2.5mL) under Argon, and was treated with the amine (0.085g, 0.46mmol), and was stirred at ambient temperature overnight. The completed reaction was concentrated down to afford the title compound; MS (ES+) *m/e* 580 [M+H]<sup>+</sup>.

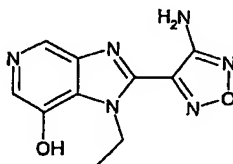
**Step 2. 4-[7-((S)-3-Amino-pyrrolidine-1-sulfonyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine**

The title compound was prepared by dissolving the product, from Step 1, in a minimal amount of MeOH, and adding 1 mL of a 1M solution of HCl in Et<sub>2</sub>O. The mixture was stirred  
 5 for 6 hours, then concentrated *in-vacuo* to dryness, taken up in DMSO, and purified via reverse-phase HPLC to give the title compound (0.0443g, 32%); MS (ES+) m/e 379 [M+H]<sup>+</sup>.

The following examples were prepared from the product of Example 279 using the method described in Example 280.

	Example	Amine	Characterisation
281	2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-sulfonic acid methylamide	Methylamine	MS (ES+) m/e 324 [M+H] <sup>+</sup>
282	2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-sulfonic acid dimethylamide	Dimethylamine	MS (ES+) m/e 338 [M+H] <sup>+</sup>

10 **Example 283: 2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-ol**

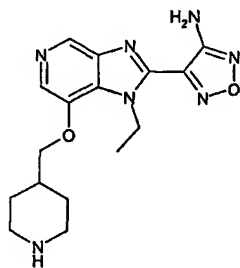


A solution of the product from Example 100 (2.6 g, 8.41mmol) in tetrahydrofuran (180ml) at –78°C was treated with a 2.5M solution of n-butyllithium (8.41ml, 21.03mmol) in hexanes. After the addition was complete the mixture was treated with trimethylborate (2.62g,



25.23mmol) and allowed to reach room temperature. After 1.5 hours at room temperature the reaction was carefully quenched with 3M aq. NaOH (12.5ml) followed by a 30% aqueous hydrogen peroxide solution (4.3ml). After 45 minutes the reaction was acidified with 2M hydrochloric acid and then applied to a SCX ion exchange column and eluted with methanol and then a mixture of methanol/0.880 ammonia (9:1). The basic fractions were then reduced and the solid residue was triturated with dichloromethane and filtered to afford the title compound, (1.2 g, 58%); MS (ES+) m/e 247 [M+H]<sup>+</sup>.

**Example 284:** 4-[1-Ethyl-7-(piperidin-4-ylmethoxy)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine

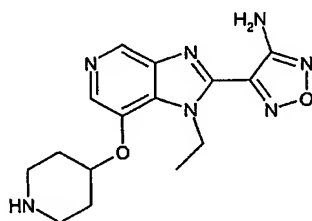


**Step 1. 4-[2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yloxymethyl]-piperidine-1-carboxylic acid *tert*-butyl ester**

A mixture of the product from Example 283 (0.1g, 0.406mmol) and K<sub>2</sub>CO<sub>3</sub> (0.112g, 0.812mmol) in acetone (3ml) at -78°C was treated with 4-iodomethylpiperidine-1-carboxylic acid *tert*-butyl ester (Villalobos, A; et al, *J. Med. Chem.*, 1994, 37(17), 2721) (0.145g, 0.447mmol) and heated at reflux for 18 hours. A further portion of 4-iodomethylpiperidine-1-carboxylic acid *tert*-butyl ester (0.145g, 0.447mmol) was then added and the heating continued for a further 6 hours. The reaction was then cooled, poured into water, extracted with dichloromethane, dried with NaSO<sub>4</sub> and reduced. The residue was chromatographed on silica gel eluting with ethyl acetate to afford the title compound, (0.071g, 39%); MS (ES+) m/e 444 [M+H]<sup>+</sup>.

**Step 2. 4-[1-Ethyl-7-(piperidin-4-ylmethoxy)-1H-imidazo[4,5-c]pyridin-2-yl]-furan-3-ylamine**

The product from Step 1 (0.071g, 0.16 mmol) was stirred in trifluoroacetic acid (0.5 ml) and dichloromethane (1ml) at room temperature for 1 hour and the solution was then co-  
5 evaporated three times with dichloromethane. The residue was purified by silica gel chromatography eluting with 0.880 ammonia:methanol:dichloromethane (1:9:90), to afford the title compound, (0.046g, 83%); MS (ES+) m/e 334 [M+H]<sup>+</sup>.

**Example 285: 4-[1-Ethyl-7-(piperidin-4-yloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-furan-3-ylamine****Step 1: 4-[2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yloxy]-piperidine-1-carboxylic acid *tert*-butyl ester**

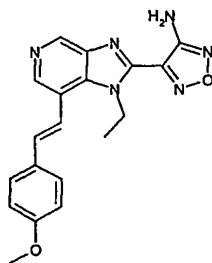
A mixture of the product from Example 283 (0.1g, 0.406mmol), 4-amino-furazan-3-yl-1-ethyl-1H-imidazo[4,5-c]pyridin-7-yloxy-piperidine-1-carboxylic acid *tert*-butyl ester (0.074g, 0.369mmol) and tributylphosphine (0.074g, 0.369mmol) in tetrahydrofuran (5ml) was treated with 1,1'-(Azodicarbonyl)-dipiperidine  
15 (0.093g, 0.369mmol) and heated at reflux for 18 hours. The reaction was then cooled to RT and then applied to a SCX ion exchange column and eluted with methanol and then a mixture of methanol/0.880 ammonia (9:1). The basic fractions were then reduced and the  
20 solid residue chromatographed on silica gel eluting with ethyl acetate to afford the title compound, (0.03g, 17%); MS (ES+) m/e 430 [M+H]<sup>+</sup>.

**Step 2: 4-[1-Ethyl-7-(piperidin-4-yloxy)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-furazan-3-ylamine**

The product from Step 1 (0.03g, 0.07 mmol) was treated according to the method of Example 284 Step2 to afford the title compound, (0.02g, 87%); MS (ES+) *m/e* 330 [M+H]<sup>+</sup>.

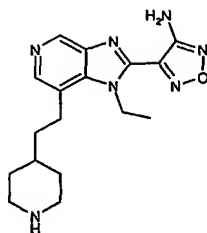
5

**Example 286: 4-{1-ethyl-7-[(*E*)-2-(4-methoxyphenyl)-vinyl]-1*H*-imidazo[4,5-*c*]pyridin-2-yl}furazan-3-ylamine**



The product of example 100 (309mg, 1mmol), 4-methoxystyrene (167 uL, 1.25mmol),  
 10 palladium (II) acetate (12 mg, 0.05mmol), o-tolyltriphenylphosphine (30mg, 0.10mmol) and  
 triethylamine (349uL, 2.5mmol) were heated at 130°C for 4 hours. The solution was  
 partitioned between ethyl acetate and water, extracting with ethylacetate (x3). Combined  
 extracts were washed with water (x3), brine, dried over anhydrous magnesium sulfate and  
 concentrated to a crude solid, 450mg, then purified by column chromatography eluting with  
 15 1:9:90 ammonia:ethanol:dichloromethane affording the title product, 176mg (49%); MS  
 (ES+) *m/e* 363 [M+H]<sup>+</sup>.

**Example 287. 4-[1-Ethyl-7-(2-piperidin-4-yl-ethyl)1*H*-imidazo[4,5-*c*]pyridin-2-yl]-furazan-3-ylamine**



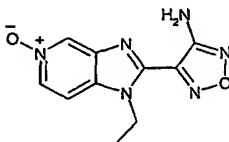
A solution of 4-vinyl-piperidine-1-carboxylic acid *tert*-butyl ester (WO 9620192) (1.2 mM; 252 mg) in dry tetrahydrofuran (4 ml) was treated with a 0.5M solution of 9-borabicyclo[3.3.1]nonane in tetrahydrofuran (1.2 mM; 2.4 ml) and stirred at room temperature for 6 hours

5 under argon. The mixture was treated with the product of Example 100 (1.0 mM; 309 mg), 1,1' bis(diphenylphosphino) ferrocene dichloro palladium (II) complex with dichloromethane (25 mg) and a 3M aqueous solution of sodium hydroxide (1 ml). The resulting mixture was heated at reflux under argon for 18 hours and purified on a 5g SCX ion exchange cartridge. After removal of the solvent *in vacuo* the resulting yellow gum was treated with trifluoroacetic

10 acid at room temperature for 2 hours and the solution passed through a 5g SCX ion exchange cartridge. The solvent was removed *in vacuo* and the residue purified on a 5g silica solid phase extraction cartridge eluting with 1-5-94 ammonia-methanol-dichloromethane to give the title compound as a white solid (23 mg). MS (ES<sup>+</sup>) m/e 342 [M+H]<sup>+</sup>.

15

**Example 288: 4-(1-Ethyl-5-oxy-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine**

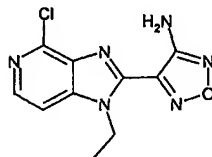


A solution of the product of Example 1 (200mg, 0.869mmol) in acetic acid (2ml) was treated with hydrogen peroxide (30%, 0.108mg, 0.957mmol) and the mixture heated 90°C for 5

20 hours. After cooling to room temperature the mixture was poured into sodium carbonate solution and extracted with dichloromethane (x4). The organic phase was dried, the solvent

was evaporated *in vacuo* and the residue purified by silica gel chromatography eluting with 15% methanol in dichloromethane, to afford the title compound (130mg, 53%); MS (ES+)  $m/e$  247  $[M+H]^+$ .

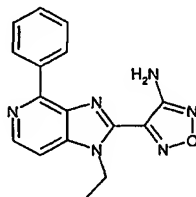
**Example 289: 4-(4-Chloro-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine**



5

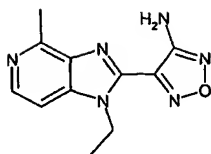
A solution of the product of Example 288 (80mg, 0.325mmol) in phosphorus oxychloride (4ml) was heated at 120°C for 6 hours. After cooling to room temperature the mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane and saturated sodium hydrogen carbonate solution. The organic phase was dried and the solvent was  
10 evaporated *in vacuo* to afford the title compound (81mg, 100%) which was used directly in the next reaction; MS (ES+)  $m/e$  265/267  $[M+H]^+$ .

**Example 290: 4-(1-Ethyl-4-phenyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)furazan-3-ylamine**



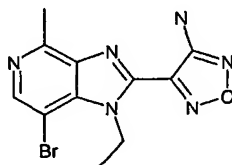
15 The title compound was prepared from the product of Example 289 and phenylboronic acid by the general method described in Example 49. MS (ES+)  $m/e$  307  $[M+H]^+$ .

**Example 291: 4-(1-Ethyl-4-methyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-furazan-3-ylamine**



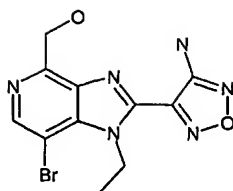
A solution of the product of Example 289 (0.1g, 0.377mmol) in 1,4-dioxan (8ml) was treated with a 2M solution of trimethylaluminium (0.378ml, 0.755mmol) in toluene and bis(triphenylphosphine)palladium (II) dichloride (0.026g, 0.0377mmol). The mixture was heated at reflux for 4 hours and then cooled to room temperature, quenched carefully with  
 5 water, poured into dichloromethane and washed with saturated sodium bicarbonate solution. The organic layer was then dried, reduced and the residue chromatographed on silica gel eluting with a mixture of dichloromethane and methanol (9.5/0.5) to afford the title compound, (0.022g, 13%); MS (ES+) m/e 245 [M+H]<sup>+</sup>.

10 **Example 292. 4-(7-Bromo-1-ethyl-4-methyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine**



The title compound was prepared from 2-methyl-3-nitro-pyridin-4-ol (*J. Med. Chem.* 1989, 32,2474-2485), using the procedures detailed in example 100 step 1, and example 36 steps  
 15 1, 2 and 3; MS (ES+), m/e 323/325 [M+H]<sup>+</sup>.

**Example 293. [2-(4-Amino-furazan-3-yl)-7-bromo-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl]-methanol**



**Step 1: 4-(7-Bromo-1-ethyl-4-methyl-5-oxy-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine**

The title compound was prepared from the product of Example 292 using the procedure  
5 detailed in example 155; MS (ES+), m/e 339/341 [M+H]<sup>+</sup>.

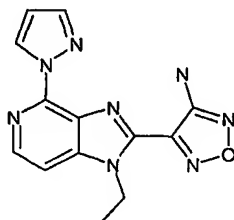
**Step 2: Acetic acid 2-(4-amino-furazan-3-yl)-7-bromo-1-ethyl-1H-imidazo[4,5-c]pyridin-4-ylmethyl ester**

10 The product of step 1 (565mg, 1.66mmol) was added to preheated acetic anhydride (5ml, 53mmol) at 110°C and stirred for 1 hour. The reaction was then cooled to RT and applied to a Mega Bond Elute SCX ion exchange column and eluted with methanol and then a mixture of methanol/0.880 ammonia (9:1). The basic fractions were reduced and the solid residue chromatographed on silica gel eluting with a mixture of dichloromethane / diethyl ether (9:1)  
15 to afford the title compound (300mg, 43%); MS (ES+), m/e 423/425 [M+H]<sup>+</sup>.

**Step 3: [2-(4-Amino-furazan-3-yl)-7-bromo-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl]-methanol**

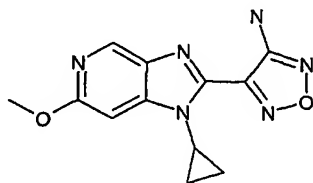
To a suspension of the product of step 2 (312mg, 0.74mmol) in methanol (10ml) was added  
20 a 2M aqueous solution of sodium hydroxide (1.1ml, 2.21mmol) and the reaction heated at reflux for 1 hour. The reaction was then diluted with water (20ml) and aged at room temperature for 2 hours. The resulting precipitate was collected, washed with water and dried *in vacuo* at 45°C for 16 hours to afford the title compound (220mg, 88%); MS (ES+), m/e 339/341 [M+H]<sup>+</sup>.

**Example 294. 4-(1-Ethyl-4-pyrazol-1-yl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine**



- 5 To a solution of pyrazole (472mg, 6.96mmol) in dimethylformamide (4ml) at 0°C was added portionwise sodium hydride (60% dispersion in mineral oil, 167mg, 6.96mmol). The reaction was then treated with a solution of the product of example 289 (200mg, 0.87mmol) in dimethylformamide (2ml) and heated at 60°C for 3 days. The reaction was cooled and diluted with ethyl acetate (25ml), then washed sequentially with saturated sodium
- 10 bicarbonate solution, water, brine, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was purified using silica gel chromatography eluting with a mixture of 0.880 ammonia:methanol:dichloromethane (5:95) to afford the title product (30mg, 12%). MS (ES<sup>+</sup>) m/e 297 [M+H]<sup>+</sup>.

15 **Example 295: 4-(1-Cyclopropyl-6-methoxy-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine**



**Step 1. 4-Methoxy-5-nitro-1H-pyridin-2-one**

- To a stirred solution of potassium *tert*-butoxide (2.8g, 25mmol) in liquid ammonia (30ml) at –
- 20 30°C was added dropwise a solution of 4-methoxy-3-nitropyridine (1.54g, 10mmol), *tert*-butyl



hydroperoxide (5M in decane, 2.2ml, 11mmol) in tetrahydrofuran (10ml) over 20 minutes. After stirring at  $-30^{\circ}\text{C}$  for 30 minutes saturated ammonium chloride solution (ca 5ml) was cautiously added and the mixture allowed to warm to room temperature. The ammonia was evaporated and the residue diluted with water (50ml). The resulting solid was collected,  
5 washed with water and dried to give the title compound (1.24g, 73%). MH (ES+) m/e 171 [M+H]<sup>+</sup>.

### Step 2. 2-Chloro-4-methoxy-5-nitropyridine

A stirred solution of phosphorous oxychloride (8ml) and N,N-diethylaniline (1.9ml, 12mmol)  
10 at  $0^{\circ}\text{C}$  was treated with the product of Step 1 (1.7g, 10mmol). The mixture was heated at reflux for 3 hours and then cooled to room temperature. The mixture was evaporated *in vacuo* and the residue co-evaporated with toluene. The residue was added to ice-water and the solution extracted with ethyl acetate. The organic phase was dried and evaporated *in vacuo* to give the title compound (1.78g, 94%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.82 (1H, s), 7.05 (1H, s),  
15 4.06 (3H, s).

### Step 3. 2,4-Dimethoxy-5-nitropyridine

A solution of the product of Step 2 (950mg, 5mmol), sodium methoxide (695mg, 12.5mmol) in methanol (10ml) was heated at reflux for 2 hours. After cooling the solvent was removed  
20 *in vacuo* and the residue partitioned between ethyl acetate and water. The organic phase was washed with water and brine, dried and evaporated *in vacuo* to give the title compound (900mg, 98%). MS (ES+) m/e 185 [M+H]<sup>+</sup>.

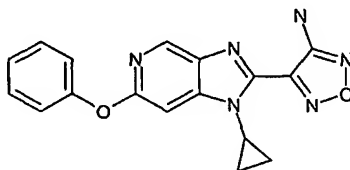
### Step 4. 4-(1-Cyclopropyl-6-methoxy-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine

25 The title compound was prepared from the product of Step 3 using the methods described in Example 2 Step 1, followed by Example 1 Steps 2-4; MS (AP+) m/e 273 [M+H]<sup>+</sup>.

**Example 296. 4-(1-Ethyl-6-methoxy-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine**

The title compound was prepared from the product of Example 295, Step 3 and ethylamine using the methods described in Example 2, Step1 followed by Example 1, Steps 2-4; MS (ES+) m/e = 261 [M+H]<sup>+</sup>.

5

**Example 297: 4-(1-Cyclopropyl-6-phenoxy-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine****Step 1. 4-Methoxy-5-nitro-2-phenoxy-pyridine**

- 10 A solution of phenol (226mg, 2.4mmol) in *N,N*-dimethylformamide (5ml) was treated with sodium hydride (144mg, 60% dispersion in oil, 2.4mmol). After stirring at room temperature for 10 minutes the suspension was added to a solution of the product of Example 295 Step 2 (377mg, 2mmol) in *N,N*-dimethylformamide (2ml). After 2 hours saturated ammonium chloride solution was added and the solution was extracted with ethyl acetate. The organic
- 15 phase was washed with water and brine, dried and concentrated *in vacuo* to give the title compound which was used directly in subsequent steps. MS (AP+) m/e 247 [M+H]<sup>+</sup>.

**Step 2. 4-(1-Cyclopropyl-6-phenoxy-1H-imidazo[4,5-c]pyridin-2-yl)furazan-3-ylamine**

- The title compound was prepared from the product of Step 1 using the methods described in
- 20 Example 2 Step 1, followed by Example 1 Steps 2-4; MS (AP+) m/e 335 [M+H]<sup>+</sup>.

**Example 298. 4-(1-Ethyl-6-phenoxy-1H-imidazo[4,5-c]pyridin-2-yl)furazan-3-ylamine**

**Step 1. 2-Chloro-4-(ethylamino)-5-nitropyridine**

A solution of 4-(ethylamino)-2-methoxy-5-nitropyridine (5.0 g, 25.3 mmol) in POCl<sub>3</sub> (25 mL) was heated to 100 °C in a sealed tube for 1 week. The reaction mixture was cooled and concentrated and the residue was taken up in EtOAc / H<sub>2</sub>O and carefully quenched with sat. K<sub>2</sub>CO<sub>3</sub>. The aqueous layer was extracted with EtOAc, washed with H<sub>2</sub>O, dried (MgSO<sub>4</sub>) and concentrated to give an orange oil which solidified on standing which was used without further purification. MS (ES+) m/e 202 [M+H]<sup>+</sup>.

**Step 2. 4-(Ethylamino)-5-nitro-2-phenoxy-pyridine**

- 10 A solution of sodium phenoxide (prepared from phenol and NaH) (6 mmol) in THF (3 mL) was added to a solution of the product from Step 1 (600 mg, 3.0 mmol) in THF (2 mL) and the resulting solution was heated to reflux overnight. The solution was cooled, poured into H<sub>2</sub>O and extracted with EtOAc. The organic layers were washed with H<sub>2</sub>O and brine, dried, filtered and concentrated to give a residue which was purified by column chromatography (5-  
15 80% EtOAc in hex) to give the title compound which was used directly in the next step. MS (ES+) m/e 260. [M+H]<sup>+</sup>.

**Step 3. 4-(1-Ethyl-6-phenoxy-1H-imidazo[4,5-c]pyridin-2-yl)furazan-3-ylamine**

- The title compound was prepared from the product of Step 2 using the methods described in  
20 Example 1 Steps 2-4; MS (ES+) m/e 323 [M+H]<sup>+</sup>.

The following compounds were prepared from the product of Example 298, Step 1, by the method of Example 298 Steps 2-3.

	Example	Phenol	Characterisation
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299	4-(1-Ethyl-6-(4-fluorophenoxy)-1H-imidazo[4,5-c]pyridin-2-yl)furan-3-ylamine	4-fluorophenol	MS (ES+) m/e 341 [M+H] <sup>+</sup>
300	N-(3-([2-(4-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-6-yl]oxy)phenyl)acetamide hydrochloride	3-acetamidophenol	MS (ES+) m/e 380 [M+H] <sup>+</sup>
301	N-(4-([2-(4-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-6-yl]oxy)phenyl)acetamide hydrochloride	4-acetamidophenol	MS (ES+) m/e 380 [M+H] <sup>+</sup>

**Example 302. 2-(4-amino-furazan-3-yl)-1-ethyl-N-phenyl-1H-imidazo[4,5-c]pyridin-6-amine**

**5 Step 1. 4-(Ethylamino)-5-nitro-2-(phenylamino)pyridine**

Online (1.4 mL, 15 mmol) was added to the product from Example 298, Step 1 (600 mg, 3.0 mmol) in THF (5 mL) and heated to reflux overnight. The solution was cooled, poured into H<sub>2</sub>O and extracted with EtOAc. The organic layers were washed with H<sub>2</sub>O and brine, dried, filtered and concentrated to give a residue which was purified by column chromatography (20-100% EtOAc in hex) to give the title compound which was used directly in the next step.

MS (ES+) m/e 259. [M+H]<sup>+</sup>.

**Step 2. 2-(4-Amino-furazan-3-yl)-1-ethyl-N-phenyl-1H-imidazo[4,5-c]pyridin-6-amine**

The title compound was prepared from the product of Step 1 using the methods described in Example 1 Steps 2-4; MS (ES+) m/e 322 [M+H]<sup>+</sup>.

5    **Example 303. 4-(1-Ethyl-6-methylsulfanyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine**

**Step 1. Ethyl-(2-methylsulfanyl-5-nitro-pyridin-4-yl)-amine**

Sodium methyl thiolate (308 mg, 4.4 mmol) was added to a solution of the product from  
10    Example 298, Step 1 (800 mg, 4.0 mmol) in DMF (20 mL). After 5 min the reaction mixture  
was poured into H<sub>2</sub>O and extracted with EtOAc. The organic layers were washed with H<sub>2</sub>O  
and brine, dried, filtered and concentrated to give an oil which solidified on standing and was  
used without further purification. MS (ES+) m/e 214. [M+H]<sup>+</sup>.

15    **Step 2. N-4-ethyl-6-methylsulfanyl-pyridine-3,4-diamine**

The title compound was prepared from the product of Step 1 using the method of Example  
177 Step 4. MS (ES+) m/e 184. [M+H]<sup>+</sup>.

**Step 3. 4-(1-Ethyl-6-methylsulfanyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine**

20    The title compound was prepared from the product of Step 2 using the method of Example 1,  
Steps 3-4. MS (ES+) m/e 277. [M+H]<sup>+</sup>.

**Example 304. 4-[1-[4-(2-Dimethylamino-ethoxy)-phenyl]-6-(4-fluorophenoxy)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine**

25

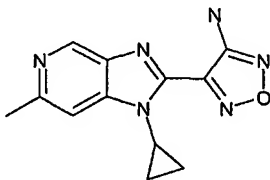
**Step 1. (2-Chloro-5-nitro-pyridin-4-yl)-(4-methoxyphenyl)-amine**

Anisole (908 mg, 7.4 mmol) was added to a solution of 2,4-dichloro-5-nitropyridine (1.30 g, 6.7 mmol) and triethylamine (1.02 mL, 7.4 mmol) in THF (5 mL). The mixture was allowed to stir at rt for 1 h, then was poured into H<sub>2</sub>O and extracted with EtOAc. The organic layers were washed with H<sub>2</sub>O and brine, dried, filtered and concentrated to a residue which was  
5 purified by column chromatography (5-50% EtOAc in hex) to give the title compound as an orange solid, 1.46 g (78%). MS (ES<sup>+</sup>) m/e 280 [M+H]<sup>+</sup>.

**Step 2. 4-[1-[4-(2-Dimethylamino-ethoxy)-phenyl]-6-(4-fluorophenoxy)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine**

10 The title compound was prepared starting from the the product of Step 1 by the method of Example 299, followed by the method of Example 38, followed by the method of Example 41. MS (ES<sup>+</sup>) m/e 476. [M+H]<sup>+</sup>.

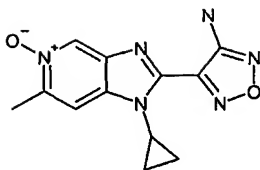
**Example 305: 4-(1-Cyclopropyl-6-methyl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine**  
15



The title compound was prepared from 2,4-dichloro-6-methyl-3-nitropyridine (R.J. Chorvat *et al.*, *J. Med. Chem.*, 1999, 42, 833-848) using the methods in Example 2 Step 1, followed by Example 1 Steps 2-4; MS (ES<sup>+</sup>) m/e 257 [M+H]<sup>+</sup>.

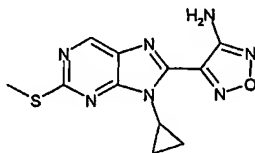
20

**Example 306: 4-(1-Cyclopropyl-6-methyl-5-oxy-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine**



A solution of the product of Example 305 (256mg, 1mmol) and *meta*-chloroperbenzoic acid (50%, 414mg, 1.2mmol) in dichloromethane (10ml) was stirred at room temperature for 1 hour. The solution was diluted with dichloromethane and the organic solution washed with aqueous sodium thiosulphate, saturated sodium bicarbonate solution, water and brine, dried and concentrated *in vacuo* to give the title compound (242mg, 89%). MS (ES+) *m/e* 273 [M+H]<sup>+</sup>.

**Example 307. 4-(9-Cyclopropyl-2-methylsulfanyl-9 H-purin-8-yl)-furazan-3-ylamine**



**Step 1. (6-Chloro-2-methylsulfanyl-5-nitro-pyrimidine-4-yl)-cyclopropyl-amine**

4,6-Dichloro-5-methylsulfanyl-5-nitro-pyrimidine (PCT Int. Appl. (2003), WO 0302544 (14.1g, 59 mmol), and triethylamine (8.2 ml, 59 mmol) were dissolved in ethanol (400 ml) containing tetrahydrofuran (50 ml) at -60°C. Cyclopropylamine (4.06 ml, 59 mmol) was added dropwise maintaining an internal temperature of -60°C and stirred slowly to room temperature over 3 hours. The solution was concentrated *in vacuo* and the residue slurried in diethyl ether. Solid triethylamine hydrochloride was filtered, washed with diethyl ether and the filtrate concentrated *in vacuo* to afford a crude solid. The solid was purified by column chromatography eluting with a gradient of 40% dichloromethane in hexane to dichloromethane, to afford the title compound (17.89g, 97%); MS(ES+) *m/e* 260/262 [M+H]<sup>+</sup>.

**Step 2. 6-chloro-N4-cyclopropyl-2-methansulfanyl-pyrimidine-4,5-diamine**

The product of step 1 (5.21g, 20 mmol) was dissolved in ethanol (150 ml) containing tetrahydrofuran (150 ml) and hydrogenated at 1 atmosphere for 5 hours at room temperature over 10% palladium on charcaol. The catalyst was filtered and the filtrate concentrated *in vacuo* to afford the title product (4.02g 87%) that was used in the next step without further purification; MS(ES+) m/e 231/233 [M+H]<sup>+</sup>.

**Step 3. (6-Chloro-9-cyclopropyl-2-methylsulfanyl)-9H-purin-8-yl)-acetonitrile**

The title product was obtained from product of step 2 using an analogous procedure to that used in example 1 step 3; MS(ES+) m/e 279/281 [M+H]<sup>+</sup>.

**Step 4. (9-Cyclopropyl-2-methylsulfanyl-9H-purin-8-yl)-acetonitrile**

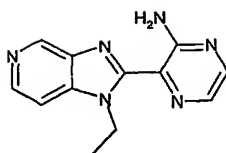
The product of step 3 (81 mg, 0.3 mmol) and zinc powder (300 mg, 4.6mmol) were heated at reflux in 3N ammonium chloride solution (10 ml) and toluene (5ml) for 48 hours. The crude mixture was filtered through celite and the filtrate extracted with ethyl acetate (x3). The combined extracts were washed with water (x3), brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford a crude solid. The solid was purified by column chromatography eluting with a gradient of hexane to ethyl acetate to afford the title compound (50 mg, 68%); <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.87 (1H s), 4.15 (2H, s), 3.29 (1H, m), 2.65 (3H, s), 1.34 (4H, m).

**Step 5. 4-(9-Cyclopropyl-2-methylsulfanyl-9 H-purin-8-yl)-furazan-3-ylamine**

The title compound was prepared from the product of step 4 using an analogous procedure to that used in example 1 step 4; MS(ES+) m/e 290 [M+H]<sup>+</sup>.

**Example 308: 3-(1-Ethyl-1 H-imidazo[4,5-c]pyridin-2-yl)-pyrazin-2-ylamine**

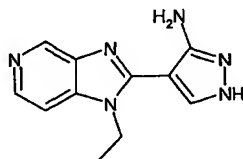




To polyphosphoric acid, preheated to 130°C, was added in one portion an intimate mixture of the product of Example 1 Step 2 (206 mg, 1.5 mmol) and 3-aminopyrazine-2-carboxylic acid (230 mg, 1.65 mmol). The temperature was increased to 195°C for 1 hour and then cooled

- 5 back to 130°C for a further 1 hour. The viscous oil was poured on to ice containing saturated sodium carbonate solution and diethyl ether (5 ml) and the aqueous solution was extracted with chloroform (x5). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude solid was purified by silica gel chromatography eluting with a gradient of dichloromethane to 0.880
- 10 ammonia:ethanol:dichloromethane (1:9:40), to afford the title compound, (20mg, 6%); MS(ES+) m/e 241 [M+H]<sup>+</sup>.

**Example 309: 4-(1-Ethyl-1H-imidazo[4,5-c]pyridin-2-yl)-1H-pyrazol-3-ylamine**



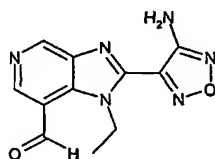
15 **Step 1. Dimethylamino-(1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl)-acrylonitrile**

The product of Example 1 Step 3 (334mg, 1.8mmol) and *N,N*-dimethylformamide dimethylacetal (214mg, 1.8mmol) in *ortho*-xylene (4ml) was heated under reflux for 45 min. After cooling, the solution was concentrated and the residue co-evaporated with toluene (x3) to afford the title compound which was used directly in the next step; MS (ES+) m/e 242

- 20 (M+H)<sup>+</sup>.

**Step 2. 4-(1-Ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-1*H*-pyrazol-3-ylamine**

The product of Step 2 (217mg, 0.9mmol) and hydrazine hydrate (90mg, 1.8mmol) in methanol (5ml) was heated under reflux for 5 hours. After cooling, the reaction mixture was concentrated and the residue purified by silica gel chromatography eluting with 0.880  
5 ammonia:ethanol:dichloromethane (1:9:90), to afford the title compound, (27mg, 13%); MS (ES+) *m/e* 229 [M+H]<sup>+</sup>.

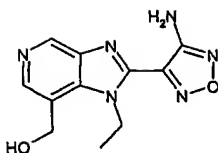
**Example 310. 2-(4-Amino-furazan-3-yl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridine-7-carbaldehyde**

10

A solution of the product from Example 100 (0.1g, 0.324mmol) in tetrahydrofuran (4ml) at –78°C was treated with a 1.6M solution of *n*-butyllithium (0.6ml, 0.97mmol) in hexanes. After 5 minutes the mixture was treated with dimethylformamide (0.3ml) and allowed to reach room temperature. After 30 minutes at room temperature the reaction was carefully  
15 quenched with water and extracted into dichloromethane (x2). The organic layer was then washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and reduced in vacuo. The residue was purified by silica gel chromatography eluting with ethyl acetate, to afford the title compound, (0.034g, 41%); MS (ES+) *m/e* 259 [M+H]<sup>+</sup>.

20

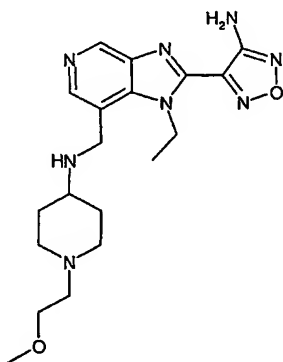
**Example 311. [2-(4-Amino-furazan-3-yl)-3-ethyl-3*H*-imidazo[4,5-*c*]pyridin-4-yl]-methanol**



A solution of the product from Example 310 (0.150g, 0.577mmol) in methanol (10ml) was treated with sodium borohydride (0.024g, 0.635mmol) and stirred at room temperature for 1 hour. The mixture was then treated with a few drops of acetic acid and then applied directly to an SCX ion exchange cartridge and washed with methanol and then a mixture of 0.880 ammonia and methanol (1:9).

The basic fractions were combined and reduced to furnish the title compound without further purification; MS (ES+) m/e 263 [M+H]<sup>+</sup>.

**Example 312. [2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-ylmethyl]-[1-(2-methoxy-ethyl)-piperidin-4-yl]-amine**



**Step 1. 1-(2-methoxy-ethyl)-piperidin-4-yl]-carbamic acid tert-butyl ester**

A mixture of piperidin-4-yl]-carbamic acid *tert*-butyl ester (500mg, 2.5mmol), potassium carbonate (621mg, 4.5mmol) and 1-bromo-2-methoxyethane (382mg, 2.75mmol) in ethanol (5ml) was heated at reflux for 18 hours. After cooling to room temperature the mixture was filtered and the filtrate concentrated *in vacuo*. Purification of the residue by silica gel

chromatography eluting dichloromethane/methanol/0.880 ammonia (100:10:1) gave the title compound (500mg, 78%); MS (ES+) m/e 259 [M+H]<sup>+</sup>.

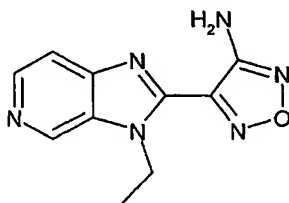
**Step 2. 1-(2-Methoxy-ethyl)-piperidin-4-ylamine**

- 5 The title compound was prepared from the product of Step 1 using the method of Example 21; (165mg, 54%); MS (ES+) m/e 159 [M+H]<sup>+</sup>.

**Step 3. [2-(4-Amino-furazan-3-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-7-ylmethyl]-[1-(2-methoxy-ethyl)-piperidin-4-yl]-amine**

- 10 The title compound was prepared from the product of Step 2 the product of Example 310 using the method of Example 149; MS(ES+) m/e 401 [M+H]<sup>+</sup>.

**Example 313 : 4-(3-ethyl-3 H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine**



15

**Step 1. Ethyl-(4-nitro-1-oxy-pyridin-3-yl)-amine**

- A solution of 3-bromo-4-nitropyrimidine-1-oxide (Daisley, R.W., Hanbali, J.R.; *Org. Prep. Proced. Int.*, 1983, 15(4), 280) (8.1g, 37mmol) in chloroform (250ml) at 0°C was teated with  
 20 ethylamine (70% aqueous solution, 25ml). After stirring at room temperature for 3 hours additional ethylamine solution (25ml) was added and stirring continued for a further 3 hours. The solution was concentrated *in vacuo* and the residue was purified by silica gel chromatography, eluting with a gradient of 10% ethylacetate/hexane to ethylacetate to afford

the title compound, (3.68g, 54%);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 8.02 (1H, d, J 7.6Hz), 7.92 (1H, d, J 1.6Hz), 7.81 (1H, br s), 7.46 (1H, dd, J=7.6, 1.6Hz), 3.32 (2H, m), 1.40 (3H, t, J 7.2Hz).

### Step 2. N-3-ethyl-pyridine-3,4-diamine

- 5 The product of step 1 (3.68g, 20mmol) was dissolved in a 1:1 mixture of ethanol:tetrahydrofuran (300ml) and hydrogenated at room temperature and atmospheric pressure using raney nickel (ca. 1g) for 18 hours. The catalyst was removed by filtration on a filter aid pad and the filtrate concentrated *in vacuo* to afford the title compound which was used without further purification, (2.72g, 99%);  $^1\text{H}$  NMR (DMSO) 7.53 (2H, m), 6.43 (1H, d, J 4.8Hz), 5.50 (2H, br s), 4.42 (1H, br s), 3.01 (2H, m), 1.21 (3H, t, J 7.2Hz)
- 10

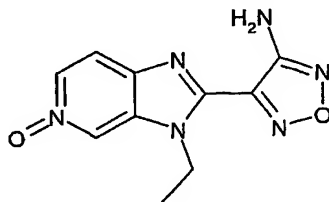
### Step 3. 3-ethyl-3H-imidazo[4,5-c]pyridin-2-yl)-acetonitrile

- The title compound was prepared from the product of step 2 using the analogous procedure to that used in example 1, step3, (1.56g, 11mmol), affording (1.09g, 49%);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )
- 15 8.88 (1H d, J 0.8Hz), 8.49 (1H, d, J 5.6Hz), 7.68 (1H, dd, J 5.6, 0.8Hz), 4.38 (2H, q, J 7.4Hz), 4.13 (2H, s), 1.59 (3H, t, J 7.4Hz).

### Step 4. 4-(3-ethyl-3H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine

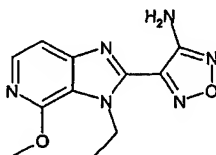
- The title compound was prepared from the product of step 2 using the analogous procedure to that used in example 1, step 4, (1.03g, 5.5 mmol) affording (240mg, 49%); MS(ES<sup>+</sup>) m/e 231  $[\text{M}+\text{H}]^+$ .
- 20

### Example 314: 4-(3-Ethyl-5-oxy-3H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine



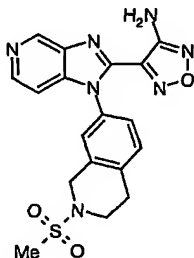
The product of Example 313, Step 4 (362mg, 1.6mmol) in acetic acid (2ml) was treated with 30%wt aqueous solution of hydrogen peroxide (432mg, 3.1mmol) and the solution was heated at 80°C for 18 hours. After cooling to room temperature the mixture was basified with solid sodium carbonate and extracted with chloroform (x5). The combined extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography eluting with 0.880 ammonia:ethanol:dichloromethane (1:9:90 ) to afford the title product, (370mg, 96%); MS(ES<sup>+</sup>) m/e 247 [M+H]<sup>+</sup>.

10 **Example 315: 4-(3-ethyl-4-methoxy-3*H*-imidazo[4,5-*c*]pyridin-2-yl)-furazan-3-ylamine**



The product of Example 314 (370mg, 1.5mmol) in phosphorous oxychloride (5ml). was heated at reflux for 4 hours. The solution was cooled and co-evaporated with toluene, the residue was basified with ice cold sodium carbonate and the aqueous solution extracted with ethyl acetate (x3). The combined extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was suspended in a solution of 50% sodium hydroxide (5ml), containing methanol (5ml) and heated at 80°C for 5 hours. The solution was concentrated *in vacuo* and the resulting wet solid that was extracted with ethyl acetate (x3). The combined extracts were washed with water (x2), brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography eluting with a gradient of dichloromethane to 0.880 ammonia:ethanol:dichlorormethane (1:9:90), to afford the title compound (30mg, 8%); MS(ES<sup>+</sup>) m/e 445 [M+H]<sup>+</sup>.

**Example 316: 4-[1-(2-Methanesulfonyl-1,2,3,4-tetrahydro-Isoquinolin-7-yl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine**



To a 0 °C solution containing 19 mg of example 97 (0.05 mmols) in 0.5 mL of dry DMF and 0.22 mL of triethylamine, was added 7 mg of methanesulfonyl chloride (0.06 mmols). The reaction mixture turned yellow. After stirring at 0 °C for 30 min., the reaction mixture was partitioned between 5 mL water and 10 mL of EtOAc. The organic layer was washed with water (2 X 5 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting residue was purified by Gilson reverse-phase HPLC to yield the title compound (3 mg, 14%).

MS (ES+) m/e 412 [M+H]<sup>+</sup>

### Pharmacy Examples

#### Tablets

a)	Compound of the invention	50.0mg
	Lactose	70.0mg
	Microcrystalline Cellulose	70.0mg
	Cross-linked polyvinylpyrrolidone	8.0mg
	Magnesium Stearate	<u>2.0mg</u>
	Compression weight	200.0mg

The compound of the invention, microcrystalline cellulose, lactose and cross-linked polyvinylpyrrolidone are sieved through a 500 micron sieve and blended in a suitable mixer. The magnesium stearate is sieved through a 250 micron sieve and blended with the active blend. The blend is compressed into tablets using suitable punches.

b)	Compound of the invention	50.0mg
	Lactose	120.0mg

Pregelatinised Starch	20.0mg
Cross-linked polyvinylpyrrolidone	8.0mg
Magnesium Stearate	<u>2.0mg</u>
Compression weight	200.0mg

5 The compound of the invention, lactose and pregelatinised starch are blended together and granulated with water. The wet mass is dried and milled. The magnesium stearate and cross-linked polyvinylpyrrolidone are screened through a 250 micron sieve and blended with the granule. The resultant blend is compressed using suitable tablet punches.

#### 10 Capsules

a)	Compound of the invention	50.0mg
	Lactose	148.0mg
	Magnesium Stearate	<u>2.0mg</u>
	Fill weight	200.0mg

15 The compound of the invention and pregelatinised starch are screened through a 500 micron mesh sieve, blended together and lubricated with magnesium stearate, (meshed through a 250 micron sieve). The blend is filled into hard gelatine capsules of a suitable size.

b)	Compound of the invention	50.0mg
20	Lactose	132.0mg
	Polyvinylpyrrolidone	8.0mg
	Cross-linked polyvinylpyrrolidone	8.0mg
	Magnesium Stearate	<u>2.0mg</u>
	Fill weight	200.0mg

25 The compound of the invention and lactose are blended together and granulated with a solution of polyvinylpyrrolidone. The wet mass is dried and milled. The magnesium stearate and cross-linked polyvinylpyrrolidone are screened through a 250 micron sieve and blended with the granules. The resultant blend is filled into hard gelatine capsules  
30 of a suitable size.



Injection Formulation

	% w/v
Compound of the invention	0.10
Water for injections B.P. to	100.00

5 Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted to that of maximum stability and/or to facilitate solution of the compound of the invention using dilute acid or alkali or by the addition of suitable buffer salts.

Solubilisers, such as cosolvents, may also be added to facilitate solution of the compound of the invention. Antioxidants and metal chelating salts may also be  
 10 included. The solution is clarified, made up to final volume with water and the pH remeasured and adjusted if necessary, to provide 1mg/ml of the compound of formula (I).

The solution may be packaged for injection, for example by filling and sealing in ampoules, vials or syringes. The ampoules, vials or syringes may be aseptically filled  
 15 (e.g. the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions) and/or terminally sterilised (e.g. by heating in an autoclave using one of the acceptable cycles). The solution may be packed under an inert atmosphere of nitrogen.

Preferably the solution is filled into ampoules, sealed by fusion of the glass  
 20 and terminally sterilised.

Further sterile formulations are prepared in a similar manner containing 0.05, 0.20 and 0.5% w/v of the compound of the invention, so as to provide respectively 0.5, 2 and 5mg/ml of the compound of the invention.

25 Biological Activity

#### Rho-kinase Activity

Using the test procedure described in the specification the compounds of the examples where found to have a pIC<sub>50</sub> in the range 9 to 5.2

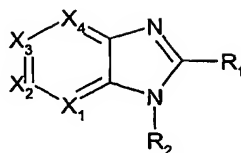
#### Msk-1 Activity

- 5 The compounds of the examples have a pIC<sub>50</sub> value in the range of 9.28 to 5.15

The compounds of the invention are essential non- toxic at therapeutically useful doses. Thus no adverse effects were observed when compounds of the invention have been administered to rats at a dose of 10mg/kg.

## Claims

1. A compound of the general formula (I)



(I)

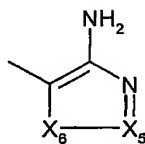
5

and physiologically acceptable salts and or N-oxides thereof wherein,

$X_1$  is N or  $CR_3$ ;  $X_2$  is N or  $CR_4$ ;  $X_3$  is N or  $CR_5$ ;  $X_4$  is N or  $CR_6$ .

with the proviso that at least one but not more than two of  $X_1$ ,  $X_2$ ,  $X_3$  and  $X_4$  represents N.

$R_1$  is a 5-, or 6- membered heterocyclic group selected from group a, b, c or d

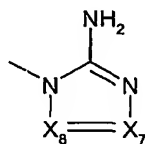


(a)

10

wherein  $X_5$  is a group selected from N or  $CR_7$  and  $X_6$  is a group selected from O, S or

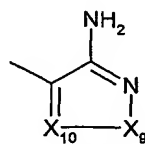
$NR_8$ ;



(b)

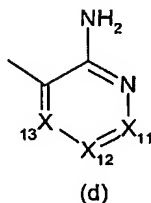
wherein  $X_7$  and  $X_8$  which may be the same or different is a group selected from N or  $CR_9$ ;

15



(c)

wherein  $X_9$  is a group selected from O, S or  $NR_8$  and  $X_{10}$  is N or  $CR_{10}$ ;



wherein  $X_{11}$ ,  $X_{12}$  and  $X_{13}$  may be the same or different and selected from a group N or  $CR_{11}$ ;

$R_2$  and  $R_8$  independently represents hydrogen, hydroxy, aryl, heteroaryl,  $C_{3-7}$ cycloalkyl, heterocyclyl, a group  $YR_{12}$ ,  $N=R_{13}$ ,  $CONR_{14}R_{15}$ ,  $COCH_2NR_{19}R_{20}$ ,  $NR_{14}COR_{16}$ ,

$SO_2NR_{14}R_{15}$  or  $C_{1-6}$ alkyl [optionally substituted by a group selected from optionally substituted phenyl,  $C_{3-7}$ cycloalkyl, heteroaryl, heterocyclyl, acylamino,  $NH_2$ ,  $R_{19}NH$ ,

$R_{19}R_{20}N$ ,  $SO_2NR_{14}R_{15}$ ,  $CONR_{14}R_{15}$ ,  $NR_{14}COR_{16}$ ,  $OalkNR_{19}R_{20}$ ,  $SalkNR_{19}R_{20}$  or  $NR_{17}SO_2R_{18}$  group];

$R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$ ,  $R_9$ ,  $R_{10}$  and  $R_{11}$  independently represent a group selected from hydrogen, halogen, hydroxy,  $R_{19}O$ ,  $R_{19}S(O)_n$ ,  $NH_2$ ,  $R_{19}NH$ ,  $R_{19}R_{20}N$ , nitro, formyl,  $C_{1-4}$ alkanoyl, alkenyl (optionally substituted by optionally substituted phenyl, heterocyclyl, or

heteoaryl), carboxy, optionally substituted phenyl, heteroaryl, cycloalkyl, cycloalkylalkyl, aryloxy, heteroaryloxy, heterocyclyl,  $CONR_{14}R_{15}$ ,  $NR_{14}COR_{16}$ ,  $SO_2NR_{14}R_{15}$ ,

$NR_{17}SO_2R_{18}$  or  $C_{1-6}$ alkyl [optionally substituted by a group selected from optionally substituted phenyl,  $C_{3-7}$ cycloalkyl, heteroaryl, heterocyclyl,  $NH_2$ ,  $R_{19}NH$ ,  $R_{19}R_{20}N$ , acylamino, hydroxy,  $CONR_{14}R_{15}$ ,  $NR_{14}COR_{16}$ ,  $SO_2NR_{14}R_{15}$ ,  $NR_{17}SO_2R_{18}$ ,

$OalkNR_{19}R_{20}$ , or  $SalkNR_{19}R_{20}$  group];

$R_{19}$  and  $R_{20}$  independently represent a group selected from  $C_{1-6}$  alkyl,  $C_{3-7}$ cycloalkyl,  $C_{3-7}$ cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl; Y represents O,  $NH$ ,  $NR_{12}$  or  $S(O)_n$ ;

$R_{12}$  represents aryl, heteroaryl, cycloalkyl, heterocyclyl or  $C_{1-6}$ alkyl [optionally substituted

by a group selected from optionally substituted phenyl, C<sub>3-7</sub>cycloalkyl, heteroaryl, heterocyclyl, NH<sub>2</sub>, R<sub>19</sub>NH, R<sub>19</sub>R<sub>20</sub>N, acylamino, hydroxy, CONR<sub>14</sub>R<sub>15</sub>, NR<sub>14</sub>COR<sub>16</sub>, SO<sub>2</sub>NR<sub>14</sub>R<sub>15</sub>, NR<sub>17</sub>SO<sub>2</sub>R<sub>18</sub>, OalkNR<sub>19</sub>R<sub>20</sub>, or SalkNR<sub>19</sub>R<sub>20</sub> group];

R<sub>13</sub> represents an alkylidene group which may be substituted by an aryl, heteroaryl, heterocyclyl or cycloalkyl group or R<sub>13</sub> represents a cycloalkylidene or heterocycloalkylidene group.

R<sub>14</sub> and R<sub>15</sub> independently represent hydrogen, aryl, heteroaryl, cycloalkyl or C<sub>1-6</sub>alkyl [optionally substituted by a group selected from optionally substituted phenyl, C<sub>3-7</sub>cycloalkyl, heteroaryl, heterocyclyl, NH<sub>2</sub>, R<sub>19</sub>NH, R<sub>19</sub>R<sub>20</sub>N, or acylamino group] or R<sub>14</sub>

and R<sub>15</sub> together with the nitrogen atom to which they are attached form a 4-7 heterocyclic ring which may be saturated or unsaturated and optionally contains another heteroatom selected from O, N or S(O)<sub>n</sub>;

R<sub>16</sub> and R<sub>18</sub> independently represent, aryl, heteroaryl,

heterocyclyl, cycloalkyl or C<sub>1-6</sub>alkyl [optionally substituted by a group selected from

optionally substituted phenyl, C<sub>3-7</sub>cycloalkyl, heteroaryl, heterocyclyl, NH<sub>2</sub>,

R<sub>19</sub>NH, R<sub>19</sub>R<sub>20</sub>N, or acylamino group] or the group NR<sub>14</sub>R<sub>15</sub> wherein R<sub>14</sub> and R<sub>15</sub> have the meanings defined above;

R<sub>17</sub> represents hydrogen, aryl, heteroaryl, heterocyclyl, cycloalkyl or C<sub>1-6</sub>alkyl [optionally substituted by a group selected from optionally substituted phenyl, C<sub>3-7</sub>cycloalkyl,

heteroaryl, heterocyclyl, NH<sub>2</sub>, R<sub>19</sub>NH, R<sub>19</sub>R<sub>20</sub>N, or acylamino group];

Alk is a C<sub>2-4</sub> straight or branched alkylene chain

n is zero, 1 or 2.

2. A compound as claimed in claim 1 wherein only one of X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub> or X<sub>4</sub> represents N.

3. A compound as claimed in claim 2 wherein X<sub>2</sub> or X<sub>3</sub> represent N.

4. A compound as claimed in any of claims 1 to 3 wherein X<sub>3</sub> represents N.

5. A compound as claimed in claim 1 wherein X<sub>1</sub> and X<sub>3</sub> each represents N.

6. A compound as claimed in any of claims 1 to 5 wherein  $R_1$  is a group selected from (c) or (d).
7. A compound as claimed in any of claims 1 to 6 wherein  $R_1$  is a group (c) in which  $X_9$  is oxygen and  $X_{10}$  is nitrogen.
- 5 8. A compound as claimed in any of claims 1 to 7 wherein  $R_2$  represents hydrogen,  $C_{1-6}$ alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-7}$  cycloalkylmethyl, phenyl or phenyl substituted by ( amino, dialkylamino, dialkylaminoalkylamino, alkyl, alkanoyl, alkoxy, halo, hydroxy, aminoalkyl, hydroxalkoxy, aminoalkoxy, alkylaminoalkoxy, N-alkyl-Nalkylaminoalkoxy, aminocarbonylalkoxy, alkylaminocarbonylalkoxy, dialkylaminocarbonylalkoxy, ureidoalkoxy, alkylureido, dialkylamino-acetamido, alkylthioalkoxy, phenylthioalkoxy, alkylsulphinylalkoxy, phenylsulphinylalkoxy, alkylsulphonylalkoxy, phenylsulphonylalkoxy, cyanoalkoxy, acylaminoethoxy, alkylsulphonylaminoalkoxy, phenylsulphonylaminoalkoxy, alkoxycarbonylalkoxy, heterocyclalkoxy, heterocycloxy, heterocyclyl), alkyl substituted by ( hydroxy, amino, acylamino,  $R_{19}NH$ ,  $R_{19}R_{20}N$ , a 4-7-membered heterocyclyl group), a 4-7 membered heterocyclyl group, a 5,6 fused bicyclic heteroaryl group, a 6,6 fused bicyclic heterocyclic group, a 6,5 fused heterocyclic group or a 6,7 fused heterocyclic group.
- 9 A compound as claimed in any of claims 1 to 8 wherein  $R_2$  represents hydrogen, methyl, ethyl, isopropyl, sec butyl, 2-ethylbutyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopropylmethyl, cyclohexylmethyl, phenyl, phenyl substituted by [ amino, 4 - dimethylamino, dimethylaminoethylamino, N-methyl, dimethylaminoethylamino, N,N-bis(2-dimethylaminoethyl)amino), ethyl, acetyl, methoxy, 3-methylbutoxy, chlorine, bromine, hydroxy, aminomethyl, 2-hydroxyethoxy, 3-hydroxypropoxy, 2- aminoethoxy, 2-methylaminoethoxy, 2-dimethylaminoethoxy, 2 diethylaminoethoxy, 2 diethylamino-1-methylethoxy, 2-disopropylamino-1-methylethoxy, N N-benzyl N-methylaminoethoxy, aminocarbonylmethoxy, aminocarbonyl-2-methylethoxy, aminocarbonylethoxy, methylaminocarbonylmethoxy, dimethylaminocarboxymethoxy, ureidomethoxy, 3-
- 10
- 15
- 20
- 25

- methylureido, dimethylaminoacetamido, methylthiomethoxy, phenylthiomethoxy, methylsulphinylmethoxy, phenylsulphinylmethoxy, methylsulphonylmethoxy, phenylsulphonylmethoxy, cyanomethoxy, 2-cyanoethoxy, t-butoxycarbonylaminoethoxy, isoxazolylaminoethoxy, isonicotinylaminoethoxy, methylsulphonylaminoethoxy,
- 5 phenylsulphonylaminoethoxy, 2-methoxycarbonyl 1-methylethoxy, morpholinoethoxy, piperidinoethoxy, 1-pyrrolidino-2-ylmethoxy, 1-methyl-piperidino-4-yloxy or 3-pyrrolidinyl,] 2-hydroxy-1-methyl-ethyl, 3-aminopropyl, 4-aminobutyl, 5 aminopentyl, 4-butyloxycarbonylamino-butyl, 2-dimethylamino-1-methylethyl, 4-diethylamino-1-methyl-butyl, 3-dimethylaminopropyl, 4-methylpiperazin-1-ethyl, 2-piperazin-yl-ethyl, piperidine 4-yl
- 10 methyl, piperidine 3-yl methyl, piperidin-4-yl, piperidin-3-yl, pyrrolidin-3-yl, 5-indazolyl or 6-indazolyl, tetrahydroisoquinolin-5-yl, 2-methyl tetrahydroisoquinolin-7-yl, 2-methanesulphonyl-tetrahydroisoquinolin-7-yl, tetrahydroisoquinolin-7-yl, 3,4 dihydro-2H-isoquinolin-1-one-7-yl, 2,3-dihydro-1H-isoindol-5-yl, benzo[1,3]dioxol-5-yl or 2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yl
- 15 10 A compound as claimed in any of claims 1 to 9 wherein  $R_3$  represents hydrogen, halogen, hydroxy, carboxyl, phenyl or phenyl (substituted by one or two groups selected from alkoxy, hydroxy, hydroxymethyl, trifluoromethyl, trifluoromethoxy, amino, acetamido, aminoalkyl, alkyl, carboxyl carboxamido, N,N-dimethylcarboxamido, cyano, formyl, phenoxy,
- 20  $CH_3S(O)_n$  wherein n is zero, 1 or 2,  $CH_3SO_2NH$ , or halogen), or heterocyclyl, heteroaryl, 6,5-fused bicycloheterocyclyl, an optionally substituted phenyl substituted by the group  $CH_2NR_{19}R_{20}$  wherein  $R_{19}$  is alkyl, phenyl or a heterocyclic group and  $R_{20}$  is hydrogen or methyl, or  $NR_{19}R_{20}$  is a 4-7 heterocyclic group, alkyl substituted by (a 4-7 membered heterocyclyl group or a group  $NR_{19}R_{20}$  (wherein  $R_{19}$  is hydroxylalkyl, optionally substituted
- 25 benzyl, C<sub>3-7</sub> cycloalkyl, a heterocyclic group, a 4-7 membered heterocyclalkyl or C<sub>3-7</sub> cycloalkylalkyl,  $R_{20}$  is hydrogen, methyl or acetyl),

4-heterocycloxy, heterocyclalkoxy, vinyl (optionally substituted by optionally substituted phenyl),  $\text{CONR}_{14}\text{R}_{15}$

wherein  $\text{R}_{15}$  is hydrogen,  $\text{R}_{14}$  is benzyl, phenethyl, aminoalkyl, 4-7 membered heterocycl or 4-7 membered heterocyclalkyl, or  $\text{R}_{14}$  and  $\text{R}_{15}$  together with the nitrogen atom to which they are attached represent a 4-7 membered heterocycl group, a group  $\text{R}_{19}\text{S}(\text{O})_n$  (wherein  $n$  is zero, 1 or 2 and  $\text{R}_{19}$  is optionally substituted phenyl), or a group  $\text{R}_{19}\text{NH}$  and  $\text{R}_{19}$  is optionally substituted phenyl or heteroaryl.

11 A compound as claimed in any of claims 1 to 10 wherein  $\text{R}_3$  represents hydrogen, bromine, hydroxy, carboxyl, phenyl or phenyl (substituted by one or two groups selected from methoxy, ethoxy, hydroxy, hydroxymethyl, trifluoromethyl, trifluoromethoxy, amino, acetamido, aminomethyl, aminoethyl, methyl, ethyl, carboxyl, carboxamido, N,N-dimethylcarboxamido, cyano, formyl, phenoxy,  $\text{CH}_3\text{S}(\text{O})_n$  wherein  $n$  is zero, 1 or 2,  $\text{CH}_3\text{SO}_2\text{NH}$ , or fluorine), 5-methyl-1,2,4-oxadiazol-3-yl, 2-thienyl, 4-methylthienyl, 5-phenylthienyl, 5-formylthienyl, or 3-thienyl, 2-furanyl, pyridyl such as 3-pyridyl or 4-pyridyl, 15 3,5-dimethylisoxazol-4-yl, indolyl or 8-quinolyl, benzothienyl, 5-benzo[1,3]dioxolyl, a phenyl or fluorophenyl substituted by the group  $\text{CH}_2\text{NR}_{19}\text{R}_{20}$  (wherein  $\text{NR}_{19}\text{R}_{20}$  represents ethylamino, dimethylamino, 4-morpholino, pyrrolidino, piperidino, piperidin-4-yl-amino or 1-t butoxycarbonyl-piperidin-4-yl-amino.), 3-hydroxypropylamino, 4-bromobenzylamino, 4-methoxybenzylamino, 4-piperidinylaminomethyl, N-4-piperidinyl-N-methylaminomethyl, 1-t 20 butoxycarbonyl-piperidinyl-aminomethyl 4-aminopiperidinomethyl, 1,4-diazepan-1-ylmethyl, piperazinomethyl, 4-methylpiperazinomethyl, 4-acetylpiperizin-1-ylmethyl, 4-ethylpiperazinomethyl 4-morpholinomethyl, piperidinomethyl, 4-(methylamino)piperidinomethyl, 4-cyclopropylaminopiperidinomethyl, pyrrolidinomethyl, 3-dimethylaminopyrrolidinomethyl, 2-hydroxymethylpyrrolidinomethyl, 4-ethylpiperazino-methyl, 3-pyrrolidin-1-yl-propylaminomethyl, 4-(4-fluorophenyl) piperazinomethyl, 3-piperidinyl-1-yl-propylaminomethyl, 3-morpholin-4-yl-propylaminomethyl, 3-(4-methylpiperazin-yl



- propylaminomethyl, 1-methyl piperidin-4-yl-aminomethyl, 4-pyrrolidinocarbonylmethyl-  
 piperazinomethyl, 2-pyrrolidin-1-ylmethylpyrrolidinomethyl, 2-pyrrolidin-1-yl-  
 ethylaminomethyl, 3-dimethylaminopyrrolidinomethyl, 1-methyl-piperidin-4-ylaminomethyl, 1-  
 isopropyl-piperidin-4-ylaminomethyl, 3-dimethylaminopyrrolidinomethyl, 2-(morpholin-yl-  
 5 methyl)-pyrrolidinomethyl, 3-piperidin-1-yl-propylaminomethyl, 3-morpholin-4-yl-  
 propylaminomethyl, 3-(4-methylpiperazin-1-yl)propylaminomethyl, piperidin-1-  
 ylmethylpyrrolidinomethyl, 3,5-dimethylpiperazinomethyl, pyrrolidin-1-ylpiperidinomethyl,  
 pyrrolidino-3-ylaminomethyl, pyrrolidin-2-ylmethylaminomethyl,  
 4-aminomethylcyclohexylaminomethyl, 4-aminocyclohexylaminomethyl, 2-piperazin-1-  
 10 ylethylaminomethyl, 3-amino-pyrrolidinomethyl, pyrrolidino-2-ylmethylaminomethyl,  
 piperidin-4-ylmethylaminomethyl, 4-aminomethylpiperidinomethyl, 4-  
 (cyclopropylaminopiperidinomethyl,  
 3-(piperazino-1-yl) propylaminomethyl, 2-(morpholin-4ylmethyl)pyrrolidinomethyl  
 2-(piperidin-1-ylmethyl)pyrrolidinomethyl, 2-(piperazin-1-ylmethyl)pyrrolidinomethyl,  
 15 piperidin-4-ylmethyl, N-piperidin-4-yl-acetamidomethyl, piperidin-4-yloxy, or piperidin-4-  
 ylmethoxy,  
 4-methoxystyryl,  $\text{CONR}_{14}\text{R}_{15}$   
 wherein  $\text{R}_{15}$  is hydrogen,  $\text{R}_{14}$  is benzyl, phenethyl, 3-aminopropyl, 4-aminobutyl, 6-  
 aminoethyl, 3 or 4-piperidinyl 1-aminomethylcarbonyl-piperidin-4-yl, 3-pyrrolidinyl, piperidin-  
 20 2-ylmethyl or piperidin-4-ylmethyl, morpholin-2-ylmethyl or piperazinoethyl, or  $\text{R}_{14}$  and  $\text{R}_{15}$   
 together with the nitrogen atom to which they are attached represent piperazino, 1-  
 methylpiperazino, 4-(2-aminoethyl)piperazino, 4-(t-butoxycarbonylaminoethyl)piperazino, 4-  
 aminomethylcarbonylpiperazino, 4-aminoethylcarbonylpiperazino, 4-1-  
 (aminoethylcarbonylpiperazino, 4-(1-methylaminoethylcarbonylpiperazino, 4-pyrrolidin-2-yl-  
 25 carbonylpiperazino, pyrrolidino, 3-aminopyrrolidino, 2-methoxycarbonylpyrrolidino,  
 morpholino, 2 (pyrrolidin-1yl)methyl pyrrolidino, a group  $\text{R}_{16}\text{S}(\text{O})_n$  wherein  $n$  is zero, and

R<sub>19</sub> is phenyl optionally substituted by methoxy, a group R<sub>19</sub>NH wherein R<sub>19</sub> is phenyl, 4-morpholinophenyl or 3-aminopyridyl.

12 A compound as claimed in any of claims 1 to 11 wherein R<sub>4</sub> is hydrogen, methyl,  
5 methoxy, methylthio, phenylamino or phenoxy optionally substituted by fluorine or acetamido.

13 A compound as claimed in any of claims 1 to 12 wherein R<sub>5</sub> is hydrogen, methyl, methoxy or phenoxy.

14 A compound as claimed in any of claims 1 to 13 wherein R<sub>6</sub> is hydrogen, chlorine ,  
10 hydroxymethyl, methyl, methoxy, phenyl, 1- pyrrolidinyl or 1- pyrazolyl.

15 A pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt and or an N oxide thereof together with one or more pharmaceutically acceptable excipients and /or carriers .

16 A compound of formula (I) and/or physiologically acceptable salts thereof for use in  
15 therapy .

17 The use of a compound of formula (I) and/or a physiologically acceptable salt thereof in the manufacture of a medicament for inhibiting the effects of the kinase Msk-1 and or Rho-kinase 1 and or 2.

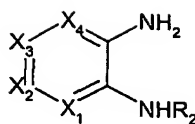
18 A method for inhibiting the effects of the kinase MSK-1 and or Rho-kinase 1 and or 2  
20 comprising administering to a patient in need thereof an effective amount of a compound of formula (I) and/or a physiologically acceptable salt thereof.

19 A process for preparing a compound of formula (I) which comprises :-

a) a process for preparing compounds of formula (I) wherein R<sub>1</sub> is a group (a), (c)

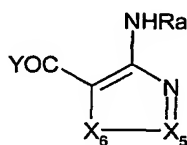
and

25 (d) by reacting the diamine (II)

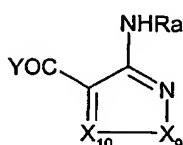


(II)

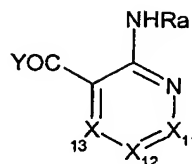
wherein  $R_2$ ,  $X_1$ ,  $X_2$ ,  $X_3$  and  $X_4$  have the meanings defined in (I) with the appropriate compound of formula (III), (IV) or (V)



(III)



(IV)



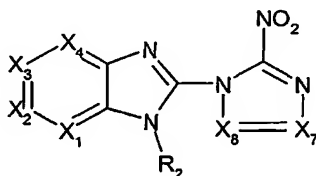
(V)

5

wherein Y is hydrogen, halogen e.g. Cl, Br or I, hydroxy or  $C_{1-4}$ alkoxy, Ra is hydrogen or a nitrogen protecting group such as an alkoxycarbonyl or benzyloxycarbonyl group and each of  $X_5$ ,  $X_6$ ,  $X_9$ ,  $X_{10}$ ,  $X_{11}$ ,  $X_{12}$  and  $X_{13}$  have the meanings as defined in formula (I) or is a group available thereto, followed when required by removal of the nitrogen protecting group Ra using conventional methods.

10

b) a process for preparing compounds of formula (I) wherein  $R_1$  is the group (b) reducing of the corresponding nitro derivative (VI)

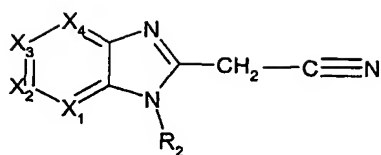


(VI)

wherein  $R_2$ ,  $R_3$ ,  $R_3$ ,  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $X_7$  and  $X_8$  have the meanings defined in formula (I).

15

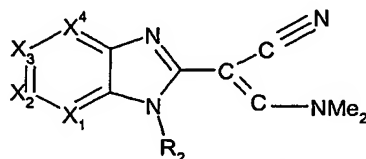
c) a process for the preparation compounds of formula (I) wherein  $R_1$  is the group (c) and  $X_9$  is oxygen and  $X_{10}$  is nitrogen may be prepared by reacting the nitrile (VII)



(VII)

wherein  $R_2$ ,  $X_1$ ,  $X_2$ ,  $X_3$  and  $X_4$  have the meanings defined in formula (I) with hydrochloric acid and sodium nitrite in a solvent and treatment of the product thus formed with a and hydroxylamine.

- 5 d) a process for preparing a compounds of formula (I) wherein  $R_1$  represent the group (c) and wherein  $X_9$  is NH and  $X_{10}$  is CH may be prepared by reacting compound (VIII)



(VIII)

wherein  $R_2$ ,  $X_1$ ,  $X_2$ ,  $X_3$  and  $X_4$  have the meanings defined in formula (I) with hydrazine.

- 10 and if necessary or desired:-

- i removal of any protecting groups
- ii converting one compound of the invention into another
- iii isolating the product of the reaction as a salt and or a solvate thereof